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The Edward Stirling Lectures.[1]

LECTURE I: TREATMENT OF HYPERTENSION.

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THE subject I have chosen for this lecture would, I believe, have had the approval of that great clinician and physiologist whose memory we are honouring tonight. Edward Stirling was essentially a physiologist with a clinical outlook, and hypertension is a clinical condition associated with disordered physiology. In recent years animal research has shed some light on the ætiology and treatment of this condition, but we are still far from a solution of the main problems involved. The experimental physiology of the production of hypertension was discussed in 1950 by a previous Stirling lecturer, and tonight I propose to discuss the treatment of the condition known as essential or idiopathic hypertension. I shall not deal with any of the types of hypertension for which causes are known other than to sound a warning that these types should be excluded before treatment for the special variety known as essential hypertension is commenced.

The normal limit of blood pressure in varying age groups is not well recognized, and an inelastic standard may lead to unnecessary treatment and invalidity. Good clinicians, recognizing the ease with which ephemeral rises of pressure occur, do not make a diagnosis of the condition unless repeated readings confirm the existence of hypertension. A reading which is constantly above 150 millimetres of mercury (systolic) and 95 millimetres (diastolic) is regarded as abnormal; but rarely does a patient require treatment for hypertension unless his systolic pressure is over 180 millimetres of mercury and his diastolic pressure 110 millimetres, or unless complicating vascular degeneration is present. Masters *et alii* (1951) have published new standards for normal pressures at different age periods and for the lower levels of hypertension. They state that existing levels are unsatisfactory, as they have been chosen largely from insurance statistics, which are based on a selected age group which is predominantly male. Examples of the standards recommended are, at the age of thirty-five to thirty-nine years, for males, systolic pressures ranging from 110 to 145 millimetres of mercury and diastolic pressures of 68 to 92 millimetres. The lower level of hyper-

[1] Delivered on August 18 and 20, 1953, at Adelaide.

tension for this age group is 160 millimetres of mercury, systolic, and 100 millimetres, diastolic. At the age of fifty-five to fifty-nine years the range is 115 to 165 millimetres of mercury, systolic, and 70 to 100 millimetres, diastolic. The lower limit of hypertension is regarded as 180 millimetres of mercury, systolic, and 108 millimetres of mercury, diastolic.

Progressive hypertension in the young is admittedly a serious condition; but the existence of high blood pressure in the elderly is compatible with normal life expectancy. It has been stated that patients over the age of fifty-five years at the time when hypertension is recognized, who have no evidence of cardiac, cerebral or renal disease, can on the average expect to live within three years of the normal life span. As no simple treatment for hypertension is available, the worst service that can be done to elderly patients with symptomless hypertension of mild degree is to inform them of their blood pressure reading. Many such patients are converted into invalids or are unnecessarily deprived of their earning capacity through unwise solicitude on the part of their physician.

Reassurance, weight reduction and mild sedation are still the main forms of treatment for the majority of hypertensive individuals. Too many elderly patients are deprived of meat and salt, with unfortunate results on their nutrition, or their pleasures are unnecessarily restricted by a complete ban on alcohol and tobacco. Drinking or smoking in excess should be frowned upon; but occasional drinking or moderate smoking has never been proved to have any effect on the production or exacerbation of hypertension. Smoking should perhaps be forbidden if there is evidence of coronary sclerosis, as there is physiological evidence that nicotine reduces coronary blood flow.

Few symptoms in hypertensive individuals are related to the hypertension *per se*, but are due to accompanying vascular degeneration. Heart failure or coronary disease is the most common cause of death. Cerebral hæmorrhage occurs in about 14% of patients and renal insufficiency in 7%. A high percentage of hypertensive patients present for the first time when one of these complications occurs, and the treatment required is that of the presenting disease.

It has long been debated whether lowering of the blood pressure could prevent the development of vascular degeneration with its consequent interference with function or whether, when vascular degeneration is preesnt, hypotensive measures would tend to precipitate extension of the pathological changes. Most forms of degeneration are irreversible; but in experimental animals it has been shown that decrease in cardiac size can be achieved if the hypertension is relieved. Until recently, as far as human beings were concerned, this was a somewhat academic argument, as there was no practicable therapeutic procedure which effectively reduced high blood pressure. The use of sympathectomy showed that in some cases lowering of the blood pressure improved cardiac, renal or cerebral circulation, and research was made for a drug that would produce the same effect.

Hypotensive agents fall into three main groups, depending on their site of action. Some drugs, such as "Veriloid", act centrally; others, such as the methonium compounds, block transmission through ganglia; while still others, such as dibenzylene, are peripheral blocking agents preventing transmission from the sympathetic nervous system to the end organ. There is as yet no really satisfactory hypotensive drug, but the ganglionic blocking agents give promise for the future. At present the methonium compounds are the most widely used, and although not very satisfactory they are the only drugs which have, in clinical practice, produced hypotension lasting for a moderate period without excessive toxic effects. It is my opinion that reduction in pressure carefully performed is of value in the treatment of patients with severe hypertension; but owing to the difficulty in controlling the drug therapy, such ganglionic blocking agents should be used only in the treatment of young patients without symptoms, with a diastolic pressure over 120 millimetres of mercury, and of those patients in whom there is evidence of cardiac, cerebral or renal damage without severe renal insufficiency, or those patients with retinal changes interfering with sight.

Ganglionic Blocking Agents.

In the four years since Paton and Zamis described the ganglionic blocking properties of the methonium group of drugs, many clinicians have treated hypertensive patients with these compounds and have published conflicting reports. Much of the conflict is caused by lack of a standard procedure in taking the pressure and by an assumption that injections of the drug can be interchanged in a fairly definite ratio of dosage with oral administration. As the main fall in pressure occurs when the patient is in the upright position, it is essential that a reliable person take the blood pressure with the patient in that position, for if the readings are taken with the patient lying down, the full effect of the drug may not be noticed, the dose may be increased and syncope may occur. In patients who are bedridden and unable to stand out of bed for estimation of the blood pressure, the readings should be taken with the patient sitting upright.

Ambulation during the period of stabilization of the drug dosage is to be preferred to bed rest, as the patients are treated with the full postural effect present and the dosage is adjusted more accurately to their subsequent degree of mobility. It is no use stabilizing a patient at rest without further instruction and then sending him home to earn his living. Just as a diabetic patient is best stabilized while ambulatory, even though for ease of management he is admitted to hospital, so hypertensive patients, who are being treated with hexamethonium, should have their dose regulated while they are up and about. In this way many of the minor discomforts that occur will be reported while the patient is under supervision, and he can be instructed as to the cause of the symptoms and the method of avoidance or relief. It is my custom to admit to hospital only patients who are suffering from congestive failure or severe renal or cerebral disease, the remainder of the hypertensive patients being treated at a clinic where a trained nurse, under supervision, organizes their management. In this way, with one person taking the readings at fixed intervals after ingestion or injection of the drug, comparable figures are obtained at each visit of the patient. The blood pressure is taken according to the suggestions of the Committee for Standardization of Blood Pressure Reading (1939).

Each patient who is deemed suitable for treatment with hexamethonium is first thoroughly investigated and if there is any suspicion of renal abnormality intravenous pyelography is undertaken. An electrocardiographic examination and fluoroscopic screening of the heart are carried out as a routine procedure. Such patients are then referred to the clinic, where it is usual to try first the effect of hexamethonium given by mouth, unless the patient is very ill and it seems wise to undertake the form of treatment which is more likely to be effective immediately; in that case, subcutaneous injections of the drug, as first suggested by Smirk, are commenced. The patient has his resting blood pressure taken and is then given one tablet of hexamethonium, and the pressure is then recorded at half-hourly intervals usually up to two hours. The main fall occurs about one hour to two hours after ingestion. If no appreciable alteration occurs, the patient is brought back the next day and the effect of two tablets is tested. If there has been an effective fall with two tablets, he is given one tablet three times a day before meals, and if there has been considerable effect with one tablet he is given half a tablet and examined again in two or three days' time. Two patients have reported the occurrence of overdosage symptoms on half a tablet three times a day, but they were both nervous individuals and their tests did not reveal any pronounced fall in blood pressure. Once an effective dose has been found, the patient is advised to continue with it; but as tolerance frequently develops, the dose may have to be increased. This is done by the trial test of an increased dose. As opposed to increased tolerance, in three patients apparently well stabilized, the tolerance decreased and the dose had to be reduced. For

this reason, although a patient has been given what appears an appropriate dose, should he complain of symptoms he should be retested (Table I). McQueen (1952) has made the same observation. For the great majority of patients the maximum dose should be four tablets three or four times a day. Any larger dose is apt to produce excessive side-effects, particularly in the gastro-intestinal tract; this

TABLE I.

Mrs. F.: Example of Decreased Tolerance to Hexamethonium Bromide.

Original Blood Pressure.[1] (Millimetres of Mercury.)[2]	Blood Pressure Before Dose. (Millimetres of Mercury.)[2]	Dose.	Blood Pressure After Dose. (Millimetres of Mercury.)[2]		
			Half an Hour.	One Hour.	One and a Half Hours.
16/12/52: 230/130	168/120	2 tablets.	154/110	168/110	184/130
22/5/53: 230/130	174/120	2 tablets.	108/80	114/88	—

[1] Original blood pressure refers to pressure before treatment was commenced.

[2] Systolic/diastolic.

[3] Blood pressure before dose refers to pressure during treatment immediately before administration of the drug.

makes it inadvisable to continue even though a satisfactory fall in pressure has occurred. Oral administration is erratic because of variations in absorption, and should the total dose be absorbed, toxic effects would occur. There is considerable individual variation in the amount of drug absorbed; approximately the same amount is excreted by patients who are receiving relatively small doses parenterally as by those receiving very much larger doses by mouth. Despite the relative inefficiency of oral administration, the condition of some patients can be successfully controlled, and a larger number in whom there is no pronounced alteration in pressure state that symptomatically they are greatly improved (Table II). The main symptom

TABLE II.

Examples of Blood Pressure Falls During Stabilization Period.

Original Blood Pressure.[1] (Millimetres of Mercury.)[2]	Blood Pressure Before Dose. (Millimetres of Mercury.)[2][3]	Dose.	Blood Pressure After Dose. (Millimetres of Mercury.)[2]		
			Half an Hour.	One Hour.	One and a Half Hours.
220/110	168/110	1 tablet.	140/100	150/104	156/108
220/130	210/115	3 tablets.	165/108	145/105	148/102
246/140	256/145	1 tablet.	204/140	235/135	182/120
250/130	230/115	1 tablet.	170/106	164/100	174/108
220/130	175/120	80 m i l l i - grammes.	156/115	164/110	160/120
258/154	220/150	75 m i l l i - grammes.	140/115	170/130	196/140
225/125	210/135	80 m i l l i - grammes.	140/110	170/122	178/120
240/150	228/150	65 m i l l i - grammes.	180/140	186/146	188/146
250/156	224/156	45 m i l l i - grammes.	150/104	160/112	180/130
230/130	212/114	55 m i l l i - grammes.	106/80	130/86	144/90
230/150	198/140	20 m i l l i - grammes.	154/104	176/120	194/128

[1] Original blood pressure refers to pressure before treatment was commenced.

[2] Systolic/diastolic.

[3] Blood pressure before dose refers to pressure during treatment immediately before administration of the drug.

relieved, as with sympathectomy, is headache. Poor renal function leads to poor excretion of the drug, and a small dose given to a patient with an increased blood urea level frequently will lead to a pronounced decrease in blood pressure and relief of headache without in any way affecting the natural course of the disease.

For example, a male patient, aged forty years, with a systolic blood pressure of 210 millimetres of mercury due to nephritis, who complained of violent headache when his dosage was one tablet a day, was relieved of his headache and his systolic blood pressure fell to 140 millimetres of mercury; but his blood urea level remained at 100 milligrammes per 100 cubic centimetres, and one year later he died of uræmia.

A rising blood urea level in a patient under treatment is of serious significance, as lowering of the blood pressure may precipitate renal failure in subjects with severe kidney damage. The death of two patients in uræmia was, I consider, accelerated by reducing the pressure.

Liver failure appears to be another cause of persistent action of the drug in small dosage, as the following case shows, although it has been stated that all the drug absorbed is excreted by the kidneys and not acted on in the body (Milne and Oleesky, 1951).

A male patient, aged fifty-five years, was admitted to hospital in gross congestive failure with hypertension with a reading of 220 millimetres of mercury, systolic, and 150 millimetres, diastolic. He had been a heavy drinker and did not respond well to rest, the administration of digitalis and mercurial diuretics or vitamin *B* injections; but after his legs had been tapped and treatment with injections of hexamethonium had been given, the congestive failure was remarkably relieved, his weight falling from 16 stone to 10 stone, and his heart decreased greatly in size (Figures I and II). After he had been given hexamethonium for three weeks he developed marked overaction of the drug that lasted for many hours, and it was found that one injection would maintain hypotension for eight to twelve hours (Table III).

TABLE III.

Prolonged Fall in Blood Pressure, Presumably Due to Liver Disease.[1]

Date.	9 a.m.: Blood Pressure. (Millimetres of Mercury.)[2]	10 a.m.: Dose of Drug. (Milligrammes.)	Blood Pressure. (Millimetres of Mercury.)[2]			
			11 a.m.	1 p.m.	5 p.m.	7 p.m.
25/10/52	180/110	120	110/70	140/90	130/80	*a*[3]
26/10/52	230/115	110	140/80	*a*[3]	120/80	*a*
29/10/52	180/120	90	140/90	130/80	130/80	110/60

[1] Original pressure, 220 millimetres of mercury (systolic) and 150 millimetres (diastolic).

[2] Systolic/diastolic.

[3] *a*, Unable to stand.

His blood urea level at this stage was 20 milligrammes per 100 cubic centimetres, and his urea concentration was normal. The results of his liver function tests were abnormal. By great reduction of the dose his pressure could be kept at normal levels and the duration of action of the drug was decreased. Clinically he made an excellent improvement while under observation, but was of the type that was unlikely to be able to continue treating himself satisfactorily.

One of the main essentials in successful treatment with hexamethonium is an intelligent patient.

Stabilization by subcutaneous injection is commenced in a dosage of 10 milligrammes and the pressure is taken, as with oral administration, at half-hourly intervals. The main fall occurs as a rule between fifteen and forty-five minutes later. If there is no pronounced reaction with this dosage a dose of 20 milligrammes is tried and then the dose is increased by 10 milligrammes at a time. When a moderate fall is obtained the patient is instructed in giving his own injections and is examined in a few days and the effect of his injection observed. It usually takes about ten to fourteen days to stabilize a patient, although further increases or, more rarely, decreases in dosage may have to be made for some months. A tuberculin syringe should be used, and as the solution of hexamethonium is 10%, the figure in hundredths on the syringe corresponds to the dosage of the drug in millimetres. One practical difficulty is that many of the available syringes are poorly made, and the markings are not etched but painted on the syringe and with use tend to wear off. One of the errors made by the inexperienced is to assume that because there has been no depressor effect with a large dose of tablets,

a large initial parenteral injection can be safely given. In my experience there is no fixed relationship between the oral and subcutaneous requirements of individual patients, although on the average, as is stated by some authors, the oral dose is ten to fifteen times greater than the parenteral dose. Occasionally, when our experience at the clinic was limited, a dose of 20 or 30 milligrammes was used initially in the treatment of a patient who had failed to respond to moderately large oral doses, and syncope was produced. This is illustrated in Table IV.

TABLE IV.

Blood Pressure Changes in Mrs. C.

Initial Pressure. (Millimetres of Mercury.)[1]	Dose of Hexamethonium.	Blood Pressure. (Millimetres of Mercury.)[1]		
		After Half an Hour.	After One Hour.	After One and a Half Hours.
230/150 230/150	4 tablets (given orally). 20 milligrammes (injected).	225/150 135/100	225/150 140/110	220/125 115/100

[1] Systolic/diastolic.

It has been our experience that the morning dose usually should be smaller than the doses at midday and in the evening. Weakness or faintness in the morning from a dose that produces no symptoms later in the day has been a common complaint of patients. This symptom is not always associated with an excessive fall in blood pressure and may in some instances, as suggested by Moyer *et alii* (1953), be due to a curare-like effect of the drug. Reduction in dosage abolishes the sensation. The difference between the effective and non-effective dose is frequently only five to ten milligrammes, and consequently injection therapy should not be used unless proper control of stabilization as has been described is instituted. Control requires only an intelligent nurse or technician who has the time to take frequent blood pressure readings in the early days of the therapy, and this should be possible in a well-organized practice. The patient requires to be examined by the doctor only twice a week, provided that the technician refers to him any difficulty that arises. Unless the physician organizes such a system, dissatisfaction with the effects of the drug is bound to occur. Visits by the patient at varying times after his injection will not give a true estimate of the effect that therapy is having. Patients require to be examined only every month when properly adjusted to the drugs. Smirk (1953) allows intelligent patients to alter their own dosage according to the production of unsteadiness on standing upright for one minute by the clock. If no swaying occurs, the drug can be increased by five to ten milligrammes. This has been our practice for the past year, and patients who have been allowed to adopt this method have managed to maintain the required dose. Such patients become quite accurate in estimating, by their sensations, whether their blood pressure is up or down.

One patient, a dentist, whose blood pressure was originally 250 millimetres of mercury, systolic, and 150 millimetres, diastolic, and who reduces it temporarily to 140 millimetres of mercury, systolic, and 100 millimetres, diastolic, after injection, knows if the fall has been greater than usual and will put off an extraction for ten minutes until she is certain that her blood pressure is at a more satisfactory level. Her intuition has been checked by the trained sister at the Dental Clinic and on other occasions by myself, and her estimate of her pressure is generally remarkably accurate.

The main objection to parenteral injection is the short action of the drug, which requires three injections a day. In some cases one dose, usually the midday dose, can be replaced by tablets; but this is unusual, as injection is rarely used in the treatment of patients who respond in any degree to oral administration. Naturally patients do not desire injections three times a day, and they should not be subjected to this procedure unless the severity of their illness merits such a course. Patients who are really ill and benefit by treatment rarely complain, and I have often marvelled at the ease with which they accept their exacting therapy.

My use of the drug extends over two and a half years, but for the first eighteen months most of the patients treated were in a public hospital or were private patients stabilized in hospital and subsequently checked at my rooms or by their referring doctors. In the past year the organization which I have described has been used, and for this reason in discussing toxic effects I propose to deal with 83 private patients examined at the clinic in conjunction with Dr. John Billings. In this group 54 were treated by oral administration of the drug and 29 by injection. The average age of the orally treated was fifty-one years and that of those treated by injection was forty-six years; 32 were males and 51 were females. Nine patients have died—three of renal failure, two of coronary occlusion, three of strokes, and another suddenly, the cause of death not being determined. Faintness of varying degrees was the commonest effect of the drug and occurred on at least one occasion in 55 of the 83 patients. In many of these patients the faintness was most common in the morning, and in a further 15 it occurred only in the morning. Faintness was not a constantly recurring symptom and in most was very slight, and it usually occurred during the period of stabilization and was not sufficient to make the patient discontinue the drug. Severe weakness and faintness were very much more common in the early stages before the administration was properly controlled. Nausea, vomiting, diarrhœa and constipation have not been very common symptoms in the past year, as the giving of large doses by mouth was not persisted with, and either parenteral therapy was commenced or the drug was discontinued. The details are set out in the following tabulation.

Number of patients, 83; number of injections, 29; number of tablets, 54.

Abdominal Symptoms: Pain, three cases; nausea, six cases; severe constipation, six cases; vomiting, three cases; diarrhœa, six cases.

Cerebral Symptoms: Headache, one case; unconsciousness, two cases; confusion, two cases; increase of cerebral symptoms, five cases; vertigo, six cases.

Cardio-vascular Symptoms: Faintness, 55 cases; morning weakness, 15 cases; "pins and needles", 10 cases; Raynaud's syndrome, two cases.

Visual Disturbances: Ten cases.

An unusual complication which I have not seen reported previously was the development of Raynaud's syndrome in two patients—sufficiently severe in one patient to require discontinuance of the drug in winter unless he was prepared to stay in bed until the main effect of the morning injection had worn off. The spasm occurred at the height of the drug's action, which was half an hour after injection or one and a half hours after oral administration. This patient was very loath to give up the drug, as the failure of the left side of his heart had been greatly relieved since he had been under treatment, and he found ultimately that the arterial spasm was less with pentamethonium. Ten patients complained of occasional "pins and needles" in the hands in the absence of any objective phenomena, and presumably this symptom was similar in causation to the more severe Raynaud's syndrome.

Of patients with previous cerebro-vascular disease, an overdose of the drug in five produced a temporary exacerbation of their neurological signs. For example, a man who walked without a limp after a hemiplegia began swinging his leg when his pressure fell too low. Another patient had a recurrence of slight aphasia. In no case did permanent cerebral damage develop from excessive hypotension. Six patients complained, among other symptoms, of pain in the chest, but in only one did this pain appear to be due to coronary ischæmia, and this patient had previous evidence of angina of effort. Visual disturbances occurred in ten patients and usually consisted of temporary blurring of vision at the height of the drug's action; in most cases they passed off in a few weeks. In

none of these patients was the visual upset sufficient to warrant the use of glasses with a "*plus*" correction. Two men complained of lack of potency, which was relieved if the drug was stopped for a day.

Results of Treatment.

This series confirmed my original view (Hayden, 1952) that patients with left ventricular failure responded extremely well to hexamethonium therapy. Such patients became less breathless, and the frequency of the attacks of nocturnal dyspnœa diminished or the attacks ceased. In some instances the heart decreased considerably in size, there was no consistent pattern of electrocardiographic change, and from the experience in patients with full exercise tolerance following coronary occlusion one would not expect the electrocardiographic tracing to be an index of functional improvement. Most patients with left ventricular failure required injections of the drug, but from the patient's point of view the annoyance was well worth while. One patient who formerly had had attacks of pulmonary œdema nearly every fortnight has not had an attack for two years since treatment was instituted. Angina is not a contraindication provided that the pressure is not lowered too suddenly, and our experience is that the effort tolerance is improved with treatment. This has been noted by other observers (for example, Moyer, 1953).

This treatment did not prevent patients with previous cerebro-vascular disease from dying from strokes during therapy, even though their headache and cardiac symptoms were relieved.

Such a short time has elapsed since the ganglionic blocking agents were introduced that it is impossible for anyone to form a long-term opinion as to whether the percentage of cerebro-vascular deaths is likely to be reduced. It may be that cerebral circuation is improved if the pressure is not reduced too low, and one patient in this series was treated, at the request of his doctor, against our better judgement, with unexpected improvement.

He was a man, aged fifty years, with apparent gross cerebral arteriosclerosis as evidenced by lack of memory and concentration, slow speech and mask-like face. He was a music teacher and had to give up teaching. After a month's treatment he resumed teaching, was quicker in his speech and was again able to type and send out his accounts. On most criteria he was a most unsuitable patient for the use of hexamethonium.

Patients with renal disease do badly, although it is possible for some of the fundal changes to improve and papilloedema may disappear. This group do badly with any form of treatment, although an occasional dramatic result has been reported following sympathectomy. In our series, as has previously been mentioned, two patients were probably precipitated into uræmia when their blood pressure was effectively lowered. Such has been the experience of other observers. I have had very little experience in treating pregnant women suffering from severe hypertension; but two patients seemed to be greatly benefited by hexamethonium and had a successful obstetrical outcome, which was not regarded as a likely result without treatment.

Mrs. C., in 1944, had high blood pressure and "kidney collapse". Labour was induced and resulted in a still-birth. In 1946 she had high blood pressure at seven months' gestation. Accidental hæmorrhage occurred and labour resulted in a still-birth. In 1949, when she was two months pregnant, bilateral sympathectomy was performed. She had a miscarriage at five months. In 1952, when two months pregnant, she was given hexamethonium, and ultimately a live baby was delivered by Cæsarean section. This patient's blood pressure had been 230 millimetres of mercury, systolic, and 150 millimetres, diastolic, and was kept by hexamethonium during pregnancy in the region of 160 to 180 millimetres of mercury, systolic, and 110 millimetres, diastolic.

Hypertension in pregnant women seems an indication for the use of the drug despite the lack of success in some reported cases (Morris, 1953). It is certain that in some pregnant women the hypertension can be greatly reduced by hexamethonium treatment; for example, a reading of 230 millimetres of mercury, systolic, and 150 millimetres, diastolic, after injection of 20 milligrammes fell in one hour to 140 millimetres of mercury, systolic, and 110 millimetres, diastolic. It is not as yet established that reduction of blood pressure *per se* will protect the fœtus.

My conclusion is that hexamethonium does not fulfil all the requirements for a suitable hypotensive drug, in that it is not free from side-effects. Its use requires great care, it very frequently needs to be given by injection, and its time of action is short. Smirk (1953) reports that "M & B 2050A" is a more suitable drug for oral use; but as subhypertensive amounts remain in the blood-stream for a longer period than hexamethonium, added difficulty is met with in deciding the later doses of the day, especially when the drug is given by injection. My experience with this drug is limited; but in two patients with negligible fall in pressure during a test period of two hours, sudden syncope occurred three hours later. It would appear that to prevent such accidents the test period during the stabilization must extend over six hours, which is not always a practicable procedure. The action of hexamethonium can be prolonged by its solution in polyvinyl pyrollidine or dextran, 20,000 molecule strength. "Vegolysin Retard"—that is, a 20% solution of hexamethonium in vinyl pyrollidine—is now available commercially and is quite a satisfactory preparation; but although it is true that on the average patients require double the dose of hexamethonium in solution, occasionally a much smaller amount is sufficient. The use of a long-acting drug has certain advantages, but the disadvantage is that if the dose is excessive the toxic results last for a correspondingly long period. For example, one patient stabilized on 25 milligrammes of hexamethonium was given the same dose in dextran instead of the slightly larger dose recommended, with the result that her blood pressure fell from 220 millimetres of mercury, systolic, and 145 millimetres, diastolic, to 110 millimetres of mercury, systolic, and 80 millimetres, diastolic, and nine hours later her systolic pressure was only 130 millimetres of mercury. Despite these difficulties, methonium compounds are at present the most effective hypotensive drugs known, and do not, unlike many other hypotensive drugs, produce tachycardia or initial stimulation of ganglia. Recently they have been combined with an antihistamine drug which also has a central action, apresoline; but it would seem that the drug's toxic effects outweigh its advantages (Khan, 1953; Moyer, 1953).

A different type of drug—*Rauwolfia serpentina*—which has been used in India for ten years has been confirmed as a mild hypertensive agent by American observers (Wilkins, 1952), and may be especially useful in nervous individuals at the menopausal age, as it is mildly hypnotic; but it seems to have the disadvantage of tending to cause increased weight. Two patients treated with this drug have responded very satisfactorily.

One patient, a woman, aged forty-five years, with an original blood pressure reading of 210 millimetres of mercury, systolic, and 110 millimetres, diastolic, and suffering from headaches, was relieved of her symptoms by three tablets of hexamethonium three times a day. For six months her blood pressure was 180 millimetres of mercury, systolic, and 110 millimetres, diastolic, falling to 160 millimetres of mercury, systolic, and 100 millimetres, diastolic, after the ingestion of tablets. The hexamethonium was discontinued and she was given one tablet of *Rauwolfia serpentina*; her blood pressure fell to 150 millimetres of mercury, systolic, and 90 millimetres, diastolic, and a week later after taking two tablets a day to 140 millimetres of mercury, systolic, and 80 millimetres, diastolic. She felt much improved, and at no time in the previous six months had such low levels been observed.

The drug was also tried on three patients with severe hypertension without much effect.

Sympathectomy.

Treatment by sympathectomy has been in force for many years, and no final opinion of its value has been given. Even with the most careful selection of cases the operation has not been extremely satisfactory, as frequently the blood pressure rises after operation; but all surgeons can quote a few cases in which improvement has been dramatic. The operation should be reserved for that group

of patients for whom the subcutaneous injection of hexamethonium was advocated—namely, young patients with progressively rising blood pressure, those with severe symptoms, those with malignant hypertension without established renal failure, and those in whom the oral administration of hexamethonium is ineffective and who are adverse to injection of the drug or are too ill, too blind or too unintelligent to manage parenteral therapy. Possibly sympathectomy should be advised rather than hexamethonium treatment for very young patients. The results are similar to those with hexamethonium. Mr. Frank Morgan, in a series of 80 consecutive cases, found that the best results were obtained in patients with cardiac failure, many of whom, by the usual criteria laid down, should have been debarred from operation. Mr. Morgan found that patients with cardiac symptoms comprised 19 of the 28 patients in whom good results occurred. Other surgeons have had similar experiences (Chavez, 1949; Morrissey, 1953).

Diets with a Low Sodium Content.

The Kempner diet of rice and fruit and diets with a sodium content below 250 milligrammes are often effective in relieving severe symptoms and lowering tension, but they are very unpleasant, and few Australian patients will continue with them for any length of time. They are suitable for the treatment of acute emergencies rather than for the permanent treatment of chronic hypertension, except as an adjunct to hexamethonium, the action of which is frequently enhanced by a low sodium intake.

My own view agrees with the unknown annotator in a recent issue of *The Lancet* that "unfortunately indefinite adherence to such a diet is only possible for obsessional patients with a substantial masochistic trait".

Acknowledgements.

My thanks are due to May and Baker, Proprietary, Limited, for supplies of their products, and to the Himalaya Drug Company, of Bombay, for their supply of *Rauwolfia serpentina*.

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PAPER CHROMATOGRAPHY OF URINE IN GALACTOSÆMIA.

By GWENDOLINE K. ROBERTSON.[1]

From the Institute of Medical and Veterinary Science, Adelaide.

THE identification of amino acids and reducing substances in urine has been greatly simplified by the use of chromatography. In 1952, Holzel, Komrover and Wilson used this method to show that the galactosuria in two cases of galactosæmia was accompanied by an amino aciduria. This paper reports the chromatographic analyses for amino acids and sugar in the urine of a month old infant with hepatomegaly and "failure to thrive".

Amino Acid Chromatography.

Urine is applied to the papers in amounts equivalent to 250 microgrammes of nitrogen, and two-way chromatograms are run in alcohol and phenol. The papers are

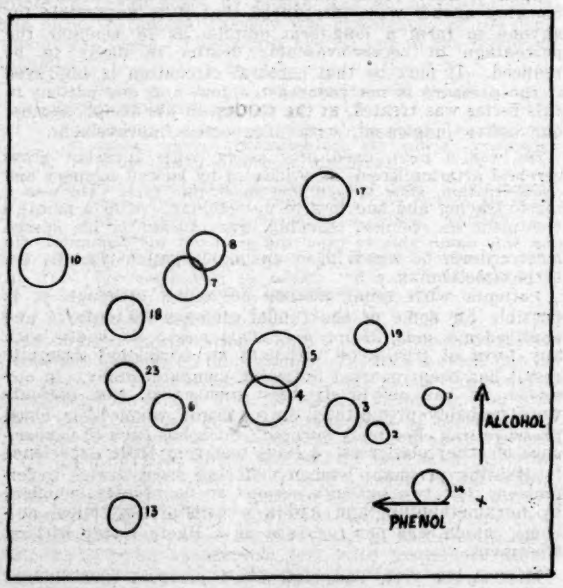

FIGURE I.
June 8, 1953: milk diet.

dipped in 0·1% ninhydrin solution in acetone, and the spots are identified by comparison with a standard map. The technical details of the method are given by Paton and Wellby (1953). The substances "17" and "19" have not been identified, but "17" is present in all normal urine and "19" is present occasionally.[2] With these two substances, it is necessary to heat the papers to above 110° C. for the ninhydrin colour to be produced, when a yellow spot edged with purple is formed. An estimate of the amount of each amino acid present is made by assigning an arbitrary number to each spot, determined by the size and intensity

[1] Receiving a grant from the National Health and Medical Research Council.

[2] Since the completion of this paper substances "17" and "19" have been identified as ammonium salts.

of the spot, and on this basis the amino acids present in the urine are given in the table.

When a milk diet was taken, both the intensity and the number of amino acids present were high. Figures I, II

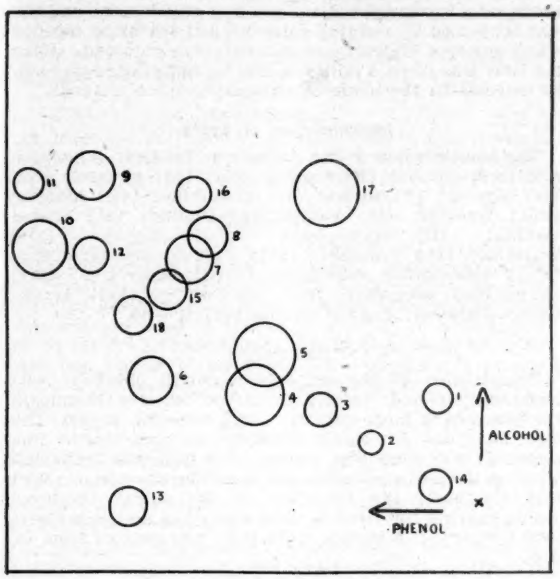

FIGURE II.
June 30, 1953: milk diet.

and III illustrate the amino acids present on June 8 and 30 and July 9 respectively. The size of the circle indicates the amount of amino acid present. Apart from the amino

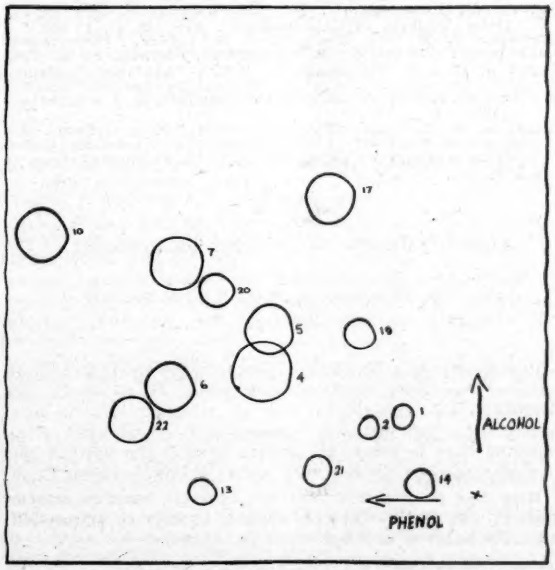

FIGURE III.
July 9, 1953: milk diet.

acids usually found in normal urine—namely, cystine, glutamic acid, glycine, serine, glutamine, alanine and sometimes threonine, histidine and tyrosine and less often the basic amino acids lysine and arginine—the following amino acids were also detected: ornithine, proline, oxyproline, phenylalanine, tryptophane, β-alanine, β-amino-iso-butyric acid and γ-amino-butyric acid.

Holzel *et alii* (1952) reported two cases in which disproportionately large quantities of serine, threonine, methylhistidine, lysine and tyrosine were found, and they suggested that this pattern might be specific for the disease. Similar although not identical patterns were found in the case under examination. Large amounts of serine and tyrosine, but no threonine, were found on June 8, and proline, oxyproline and small amounts of γ-amino-butyric acid were also present. Of the basic amino cells no lysine, but arginine and large amounts of ornithine were detected. On June 30 the same amino acids were found, and in addition small amounts of phenylalanine, valine, tryptophane, β-alanine, and β-amino-iso-butyric acid. These amino acids were not detected on July 9, but were replaced by histidine, threonine and lysine, to produce a pattern of amino acids more similar to that obtained by Holzel *et alii*. No methylhistidine was present at any stage.

After the baby had been placed on a milk-substituted diet for nearly three weeks, the pattern of amino acids had

TABLE I.

Amino-Acids.	Milk Diet.			Milk-free Diet.
	June 8.	June 30.	July 8.	July 27.
Cystine	±	±	±	±
Aspartic acid	±	±	±	±
Glutamic acid	3	1	—	±
Glycine	3	4	5	3
Serine	4	4	3	—
Glutamine	1	1	3	1
Threonine	—	—	2	±
Alanine	3	3	3	1
β-Alanine	—	3	—	—
Tyrosine	2	2	—	—
Histidine	—	—	2	±
Arginine	1	2	±	±
Lysine	—	—	±	±
Ornithine	2	1	±	±
Tryptophane	—	±	—	—
Valine	—	1	—	—
Proline	3	3	3	—
Oxyproline	1	2	—	—
Phenylalanine	—	±	—	—
β-amino-iso-butyric	—	1	—	—
γ-amino-butyric	1	—	—	—
17	2	3	2	1
19	2	—	1	1
Total	29	33	26½	11

returned to normal, as shown by Figure IV. No serine, tyrosine, proline or oxyproline was present, although there were still traces of the basic amino acids lysine and arginine. On a milk diet "17" and "19" were present in large amounts in the urine of the baby, but the intensity of these spots was considerably reduced when milk was omitted from the diet.

Sugar Chromatography.

The experimental conditions which allow the separation of amino acids are also suitable for the qualitative analysis of sugars.

Partridge and Westall (1948) give a figure in which the R_F values of a number of reducing sugars in phenol-NH_3 have been plotted as ordinates and the values in S-collidine as the abscissæ. Wolfson, Cohn and Devaney (1949) also give a map showing the position of certain sugars of clinical interest in a two-dimensional ascending chromatogram, using phenol and collidine as the solvents.

The solvents being used in this laboratory for the detection of amino acids are 80% ethyl alcohol and phenol, and a map showing the position of a number of reducing sugars in these two solvents is given in Figure V. Whatman

Number 1 filter paper is used with the racks designed by Datta, Dent and Harris (1950), five microlitres of a 1% sugar solution being applied in the lower right-hand corner. The amount of urine applied depends on the concentration of reducing sugar, which is determined by Benedict's qualitative test. Since complete reduction took place with the urine under examination, five microlitres were applied.

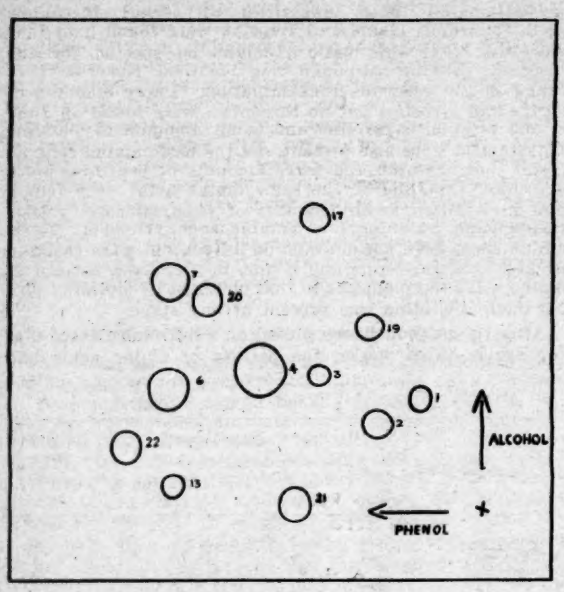

FIGURE IV.
July 27, 1953: milk-free diet.

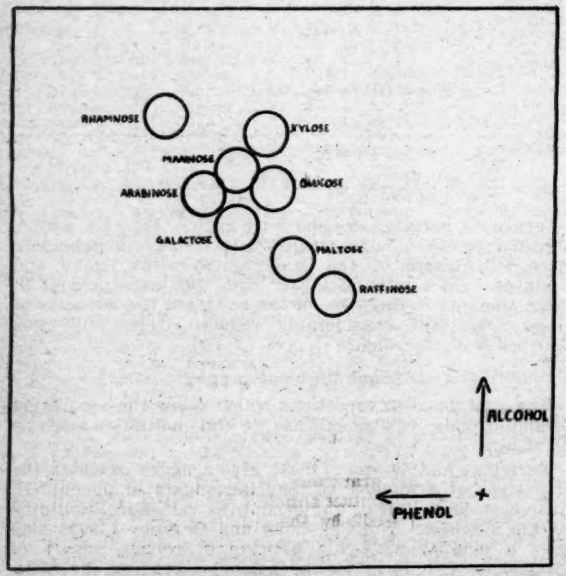

FIGURE V.

The papers are run firstly in the alcohol, dried, turned through an angle of 90° and then run in the phenol. After the excess phenol has been removed by drying, the papers are sprayed with aniline hydrogen oxalate (0·9 millilitre of aniline added to 100 millilitres M/10 oxalic acid). This produces a bright red spot with pentoses and a brown spot with galactose and glucose.

When the baby was receiving a milk diet, the urine produced a brown spot in the position of galactose, and this was confirmed by running galactose and the urine together when one spot of increased intensity was obtained. When the baby was given a milk-free diet no reducing sugar could be detected in the urine by chromatographic methods.

Identification of Spots.

The identification of the spots is as follows: (i) cysteic acid from cystine; (ii) aspartic acid; (iii) glutamic acid; (iv) glycine; (v) serine; (vi) glutamine; (vii) alanine; (viii) tyrosine; (ix) valine; (x) proline; (xi) phenylalanine; (xii) tryptophane; (xiii) arginine; (xiv) ornithine; (xv) β-alanine; (xvi) β-amino-iso-butyric acid; (xvii) unidentified substance; (xviii) oxyproline; (xix) unidentified substance; (xx) threonine; (xxi) lysine; (xxii) histidine; (xxiii) γ-amino-butyric acid.

Summary.

Examination of the urine of a month old baby with hepatomegaly and "failure to thrive" showed chemically the presence of large quantities of a reducing sugar. This was identified by chromatography as galactose. Subsequently the baby was placed on a milk-substitute diet, when galactose was no longer found in the urine. With this treatment the condition of the infant improved. Accompanying the liver damage was gross amino aciduria, which returned to normal when milk was omitted from the diet.

Acknowledgements.

The writer wishes to thank Miss Anne Carmichael for her cooperation, and the Mareeba Hospital for supplying the specimens.

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TUBAL TUBERCULOSIS AND PREGNANCY.[1]

By F. A. BELLINGHAM, M.B., B.S., M.R.C.O.G.,
Sydney.

PREGNANCY in a Fallopian tube infected by the tubercle bacillus has been reported only some 45 times in the literature.

The case of bilateral tuberculous salpingitis to be reported here is somewhat unique in that the patient had two ectopic pregnancies, with a live infant between them.

Rich has pointed out that the tubercle bacillus attacks each or one of the bilateral organs, usually in succession, and this habit is well borne out in this case.

Incidence.

Histological studies of pre-menstrual endometrial biopsies in sterility clinics have highlighted many cases of tuberculosis of the pelvis, while the antibiotics have probably cleared up more pyogenic infections. This has

[1] Read at a meeting of the Clinical Society, The Women's Hospital, Crown Street, Sydney, on December 3, 1953.

resulted in a relative increase in the number of cases of tuberculous salpingitis.

In pulmonary autopsies genital tuberculosis is found in 8% of cases, and in surgically removed adnexa in 10%.

In sterility clinics there is a great variation in the number of tuberculous infections quoted, but the accepted average is about 5%.

Of all patients with genital tuberculosis almost one-third have pulmonary lesions.

Localization.

The infection decreases from above downwards through the pelvis as follows: Fallopian tubes 95%, uterus 50%, ovaries 25%, cervix 3%, vagina and vulva very rarely affected.

Diagnosis.

The usual triad of symptoms which draws attention to genital tuberculosis consists of vague lower abdominal pains, sterility and irregularity of menstruation, tending to be "too much and too often" rather than the reverse. A tubo-ovarian mass of restricted mobility in a *nullipara* with no history of infection is highly suspicious, while in others one should be on guard when sterility is accompanied by adnexal masses that persist in spite of chemotherapy.

Treatment.

Treatment consists, in general, of surgery with preoperative and post-operative use of antituberculosis drugs.

The trend of opinion seems to be that streptomycin has been rather a disappointment.

Combinations of chemotherapeutic agents are used to prevent the emergence of drug-resistant strains of tubercle bacilli. Schaefer, at the New York Lying-in Hospital, is using streptomycin, para-aminosalicylic acid and isonicotinic acid hydrazide. The Royal College of Obstetricians and Gynæcologists in England is conducting a series in which streptomycin, one gramme, is given daily for eighty-four days with PAS, three grammes, five times daily. Vestibular disturbances and skin eruption with loss of hair have been reported but are not serious.

From the surgical viewpoint, Solomons states that removal of tuberculous tubes cures tuberculous endometritis, but there seems no point in leaving the uterus in such a case.

Report of a Case.

The patient was twenty-nine years of age when she attended me in 1949 for sterility of three years' duration. She had one child eight years of age by a previous marriage. The only significant point in the history was that of irregular menorrhagia.

On examination of the patient both tubes were found to be palpable and somewhat tender. There was an erosion of the cervix, which was cauterized.

Semen analysis showed the hsuband to be quite fertile.

Carbon dioxide failed to pass through the patient's Fallopian tubes on two occasions, and the diagnosis of "blocked tubes" was made.

A salpingogram was carried out with a good deal of pressure, and patency of the right Fallopian tube was secured. The left tube showed some probable spill. In the X-ray picture dilatation of both tubes was seen. Three months later the patient became pregnant, and in March, 1950, she had an ectopic gestation on the left side. At operation this was found to be ruptured near the cornual end of the Fallopian tube. The left tube was grossly dilated and was excised.

Microscopic examination of this tube showed typical tuberculous changes with many giant-cell systems. Tubercle bacilli were grown from this tube.

The right Fallopian tube was enlarged and covered with fine filmy adhesions. The fimbriated end was freed and a "cuff" stitched back with a couple of fine silk sutures to maintain patency.

X-ray examination of the chest showed no abnormality, and treatment consisted of general hygiene measures and a prolonged holiday. Streptomycin was not used. Convalescence was uneventful, and the patient put on weight. The result of a Rubins test was positive on the right side. Later that year she became pregnant in the uterus and she was delivered of a living male child in May, 1951.

In July, 1953, the patient again had a ruptured ectopic pregnancy, this time in the right Fallopian tube. Salpingectomy was performed and she needed several bottles of blood. Her condition did not warrant hysterectomy. Examination of the tube showed a pronounced adenomatous proliferation of the mucosal folds, but no giant-cell systems were demonstrated.

Comment.

This case is reported because of the unusual accompaniment of tuberculosis of the pelvis and pregnancy. Tuberculosis of the Fallopian tubes with two ectopic pregnancies must indeed be a rarity—more particularly so when a normal full-term uterine pregnancy is placed between those two catastrophes.

If the ovum entered the first (left) Fallopian tube before that ectopic gestation, it descended through a hydrosalpinx which was nearly closed in its lumen. If the ovum migrated across from the right tube to enter the left tube and become implanted there, the event seems even more remarkable. The patient is on holidays at present, after another negative chest X-ray examination result, but on her return a full premenstrual curettage will be carried out to search for tuberculous endometritis.

A HISTOLOGICAL STUDY OF LYMPHOID TISSUES IN ADRENALECTOMIZED RATS AFTER THE INJECTION OF A CASEIN HYDROLYSATE, "AMPARON".[1]

By L. A. G. HISSINK, M.D.,

From the Department of Pathology, Prince Henry Hospital, Sydney.

HÆMATOLOGICAL reactions with eosinopenia, neutrophilia and a relative lymphopenia in adrenalectomized rats, and eosinopenia, neutropenia and a slight absolute lymphopenia in hypophysectomized rats after the intraperitoneal administration of the casein hydrolysate "Amparon" showed some resemblance to reactions observed after the injection of cortisone in such animals (Hissink, 1953*a*, 1953*b*). This may indicate that such reactions are not specific for this steroid. It could, however, also reflect "cortisone-like" properties in the hydrolysate. To obtain evidence in favour of either of these views, lymphoid tissue from adrenalectomized rats, some of which had received adrenaline, was compared with tissue from "Amparon"-injected and cortisone-injected adrenalectomized rats. Non-treated intact rats and intact "stressed" animals were also studied.

Experiments were based upon the fact that symptoms of lymphocytic disintegration in lymphoid tissues during or after "stress" conditions in intact animals can be abolished by adrenalectomy (Selye, 1949). However, these reactions may still be produced in adrenalectomized animals provided that suitable amounts of cortisone have been administered (Selye, 1949). They are characterized by the appearance of appreciable degrees of nuclear pyknosis and karyorrhexis in lymphoid tissues, and they may be associated with signs of inflammation (Selye, 1949). Selye (1949) pointed out that the likelihood of finding karyopyknosis is greatest in the thymus.

MATERIAL AND METHODS.

Rats of Wistar origin were used, both male and female, weighing 150 to 200 grammes. The following groups were examined: Group A—intact animals: (i) untreated controls, (ii) animals "stressed" by the subcutaneous injection of one to three millilitres of 5% formol-saline solution or by being bled from the inferior *vena cava*, after which their appendices were scalded in water at 75° C. for three to five seconds; Group B—adrenalectomized animals: (i)

[1] "Amparon", manufactured by N.V. Organon, Holland, is stated to be an enzymically prepared casein hydrolysate which contains nitrogen equivalent to 2·5% protein, 3% glucose, 0·3% sodium chloride and 0·02% potassium chloride.

untreated controls; (ii) animals treated with intraperitoneal injections of 0·1 milligramme of adrenaline in one millilitre of 0·9% sodium chloride solution; (iii) animals treated with intraperitoneal injections of 0·9 milligramme of cortisone acetate in one millilitre of 0·9% sodium chloride solution; (iv) animals treated with intraperitoneal injections of one millilitre of "Amparon", an enzymically prepared casein hydrolysate (Organon, Holland).

All animals were killed by an overdose of chloroform, the "stressed" rats being sacrificed three hours or more after the induction of trauma. Adrenaline-injected and "Amparon"-injected rats were killed three hours after the injections, while those treated with cortisone were sacrificed about five hours after the injections (Dougherty and Kumagai, 1951). Tissues were fixed in Bouin's solution for half an hour and then for one or two days in 10% formol-saline. They were stained with hæmatoxylin-eosin.

Results.

In these experiments the histological studies of lymphoid tissues have been carried out in two parts: (i) examination of the general features of the thymus tissues of the various animals; (ii) examination of the occurrence of karyopyknosis in thymus and other lymphoid tissues of the animals.

Group A.

Intact Controls.

Figure I represents the histological features of sections through the thymuses of intact control rats. Macroscopically and microscopically (low magnification), medulla and cortex are easily distinguishable parts of the thymus. Under high magnification it appears that in most instances the centre of the medulla contains relatively small numbers of thymocytes. This number of thymocytes gradually increases towards the cortex, which is characterized by a denser population. Demarcations between medullar and cortical populations are not sharply defined, but the transition from one section to the other of thymus tissue is rather abrupt. Thymocytes of medulla and cortex show regularly shaped and uniformly stained nuclei, but many cells in the medulla are characterized by a certain degree of nuclear polymorphism (differences in size, irregularities in outline and variations in the intensity of staining qualities). A number of medullar macrophages show symptoms of phagocytosis, and they may sometimes be found together with small aggregations of nuclear debris.

Intact "Stressed" Animals.

Figure II represents a section through the thymus of a "stressed" rat. In 10 out of 13 rats similar pictures were found. The medulla and cortex of the thymuses are macroscopically and microscopically (low magnification) often not clearly distinguishable. Under high magnification it may be seen that both parts of the organ have altered rather significantly in the density of thymocyte populations. While the cortex shows a decrease in the number of such cells, the medulla contains appreciable numbers of them. The boundaries of the sections are masked by these alterations. The thymocytes in the medulla and cortex show uniformly shaped and stained nuclei; but many cells in the medulla have nuclei which differ in size, show irregular outlines and vary in staining qualities. Phagocytizing macrophages and small aggregations of nuclear debris can be found in the medulla.

Group B.

Adrenalectomized Controls.

Figure III shows a typical picture of the thymus structure in non-treated adrenalectomized rats. Macroscopically and microscopically these tissues are characterized by the sharpness of differences in thymocyte populations between cortex and medulla. It may be seen that the transition from the densely packed cortex to the relatively sparsely populated medulla is abrupt. Most of the thymocytes in cortex and medulla show uniformity in the appearance of their nuclei. Only a few macrophages contain phagocytized material, while nuclear debris is practically absent. A number of cells in the cortex show mitosis.

Adrenalectomized Animals which Received Adrenaline.

The histological features of the thymuses from the adrenalectomized animals which received adrenaline do not differ from those of non-treated adrenalectomized controls.

Adrenalectomized Animals which Received Cortisone.

The effects of cortisone on adrenalectomized animals may be studied in Figure IV. This picture represents lymphoid tissue of a thymus from an adrenalectomized rat about five hours after the intraperitoneal injection of the steroid. Macroscopically and microscopically (low magnification) it is easy to distinguish the medulla from the cortex. Under high magnification, however, it may be seen that the transition from the cortex to the medulla is characterized by a gradual decrease in the density of the thymocyte population. In some other sections more sharply defined demarcations are visible, the picture thereby being made to resemble that observed in non-treated adrenalectomized rats. Thymocytes in cortex and medulla are regularly shaped and stained; but many cells in the medulla show darkly stained nuclei, which differ in size and show irregular outlines. Phagocytizing macrophages can be found more easily in the medulla of thymuses of these rats than in those of controls, and these cells occur not infrequently in the vicinity of nuclear debris.

Adrenalectomized Animals which Received "Amparon".

The results of "Amparon" injections on adrenalectomized rats may be studied from Figure V. The medulla and the cortex of the thymuses are macroscopically and microscopically (low magnification) clearly distinguishable parts of the organ. It may be seen that differences between the parts of the thymus (high magnification) are not so clearly defined as in the thymuses of untreated controls (adrenalectomized, compare with Figure III). The transition from cortex to medulla is a gradual one. In some instances, however, sharply defined demarcations between cortex and medulla can be found in thymuses, which otherwise are characterized by less clearly visible differences between the two zones. Thymocytes in sections of the cortex and medulla are uniformly shaped and stained; but many cells in the medulla show darkly stained and smaller nuclei, often with irregular outlines. Phagocytizing macrophages occur not infrequently, and sometimes near aggregations of nuclear debris, of which slightly more is visible in these thymuses than in those of untreated controls (adrenalectomized).

Résumé.

The histological features of thymuses of adrenalectomized rats with and without adrenaline injections are the most consistent and regular of the groups studied. They are characterized by sharpness of demarcation between cortex and medulla and uniformity of thymocytes.

The thymuses of the other groups show a decreased sharpness in the differences between cortex and medulla thymocyte populations; but it seems that "Amparon"-treated and cortisone-treated adrenalectomized rats form an intermediary group between untreated adrenalectomized controls on the one side and intact animals on the other.

"Amparon"-treated animals show more resemblance in thymus features to those of adrenalectomized controls than cortisone-treated rats. It may be seen from Figures IV and V that "Amparon" and "cortisone" pictures are sometimes very similar, and Figure VI shows that some "Amparon"-treated adrenalectomized rats present a similarity of thymus tissue to that of stressed intact rats (compare Figure VI with Figure II). "Amparon"-treated and cortisone-treated adrenalectomized rats and the intact animals show various degrees of polymorphism in the appearance of thymocytes in the medulla. It is not possible to conclude from these results that the thymuses of rats which show polymorphic thymocytes also present more evidence of cellular disintegration in these tissues. Poly-

morphism in cellular properties may perhaps represent a certain degree of loss of integrity. This view is supported by the larger number of phagocytizing macrophages and more nuclear debris in the medullæ of the thymuses of these animals. Budding of lymphocytes (thymocytes) as described by Williamson (1950) may be found in this group, but also occasionally in non-treated adrenalectomized controls.

Another approach to the problem—namely, that of the determination of the percentage of animals in the various groups which show more pronounced degrees of karyopyknosis in their lymphoid tissues—gives the following results:

1. In the group of intact but "non-stressed" rats pronounced karyopyknosis was not found.

2. Of the 13 "stressed" intact rats, considerable degrees of diffusely distributed karyopyknosis were found in thymus tissues of only three animals about ten hours after the induction of stress (Figure VII). In six other animals karyopyknosis appeared only in certain areas of the cortex of thymuses (Figure VIII).

3. The group of more than 60 adrenalectomized rats with and without adrenaline treatment presented five cases in which localized karyopyknosis of a minor degree can be found in lymph glands only (Figure IX).

4. Of the five adrenalectomized rats given cortisone treatment only one rat showed some karyopyknosis of a localized type in the cortex of its thymus (Figure X).

5. In the group of 55 adrenalectomized rats which received "Amparon" treatment, 11 rats showed karyopyknosis of a localized type—mainly in the medullæ of the thymuses of five of them (Figures XI and XII), and furthermore, in the "medullæ" of lymphoid tissues other than thymus, as for instance in the lung of the rat shown in Figure XIII. Another 12 "Amparon"-treated adrenalectomized rats showed localized karyopyknosis of slighter degree, but usually more pronounced than was occasionally seen in the lymph glands of non-treated adrenalectomized controls.

Discussion.

The histological features of lymphoid tissues of the various groups of adrenalectomized and intact rats are difficult to interpret. Selye's statement (1949) that adrenalectomy abolishes the occurrence of significant degrees of stress-induced lymphocyte (thymocyte) disintegration in lymphoid tissues of such animals can be confirmed. However, it cannot be concluded that karyopyknosis is completely absent in such rats.

With regard to the occurrence of areas with cellular disintegration in lymphoid tissues, it is known that "degenerated cells" and karyopyknosis may be found in normal lymphoid tissue from "non-stressed" intact animals (Yoffey *et alii*, 1951). It is not yet known whether such findings have any relation to pituitary-adrenal activity of the animals. They may also represent the worn-out cells which have reached the end of their lifetime at a later stage than those which disintegrate under the influence of "stress factors". If different kinds of karyopyknosis occur, such reactions may be found in different parts of the body. It seems that the whole problem becomes one of a quantitative comparison of degrees of karyopyknosis in lymphoid tissues of which "baseline values" of the physiological "rest" condition are not precisely known. It should be emphasized that intact "non-stressed" animals which have been killed can no longer be considered to represent "non-stressed" organisms.

Emotional factors (Recant *et alii*, 1950) and reactions induced by the stress shortly before the death of the animals may occur with such a rapidity that certain histological repercussions may prove inevitable. It is known, for instance, that pulmonary œdema and pulmonary hæmorrhage can be produced in a matter of seconds when animals are killed by a blow on the head. Stimulation of certain hypothalamic centres is possibly the underlying mechanism (Gamble and Patton, 1951). It does not seem likely that disintegration of lymphocytes occurs in the same order of time (Dougherty and White, 1944; Dougherty and Kumagai, 1951).

In the study of karyopyknosis the normal breakdown of aged lymphocytes and of thymocytes must be distinguished from cellular disintegration during stress, and difficulties will arise if sudden increases in the production of lymphocytes lead to increased degrees of "non-stress" karyopyknosis. This, of course, depends upon the lifetime of lymphocytes and the period during which the rate of removal of cellular debris lags behind the increased load of breakdown products. There is some indication that the stress of adrenalectomy is followed by a rapid increase in the production of lymphocyte material (Dougherty and Kumagai, 1951). With regard to the normal lifetime of lymphocytes, it has been found that their life expectancy varies from 170 minutes in rats (Van Dyke and Huff, 1951) to about eight days in humans (Kline and Cliffton, 1952). This wide range may be due to differences in species, but also to irregular influences of the pituitary-adrenal system. If lymphocytes have a short lifetime (one and a half hours), it will be clear that the chances of finding increased degrees of karyopyknosis after adrenalectomy are greatest during the first few days after the operation.

Adrenalectomized rats may furthermore be in possession of appreciable amounts of adrenocortical metabolites during the first few days after operation. Kumagai and Dougherty (1950) demonstrated that cortisone was "stored" in adrenalectomized mice if adequate amounts of the steroid were administered. The presence of genuine adrenocortical material in adrenalectomized rats during the first few days after the operation depends upon the speed with which mechanisms culminating in adrenocortical stimulation will proceed after the commencement of anæsthesia and the operative procedure, and before the actual removal of adrenal glands. It has been shown that eosinopenic responses in laboratory animals cannot be abolished by the removal of the adrenals if this is done more than ten minutes after the induction of stress (Love, 1950).

These considerations favour histological studies late after adrenalectomy. However, this period is limited by the fact that accessory adrenocortical tissues in adrenalectomized rats may become active as time passes (Hissink, 1953*a*, 1953*b*). For this reason adrenalectomized rats were tested on the third post-operative day.

It must also be realized that adrenalectomized animals are characterized by a decreased resistance towards infectious and otherwise damaging influences. It is likely that this will be manifested by cellular destruction in affected tissues and probably more so in draining lymph glands.

Conclusions about the presence of karyopyknosis in lymphoid tissues of adrenalectomized rats therefore must be mainly based upon observations on thymus tissues of the animals. This does not mean that great differences which may appear eventually between the histological properties of lymph tissues other than the thymus have to be disregarded.

In these studies karyopyknosis of a localized type was found in the lymph glands of five out of about 60 non-treated or adrenaline-injected adrenalectomized rats. This cannot be regarded as representing cellular destruction under the influence of "stress factors", and caution is therefore warranted if karyopyknosis is found in such tissues in adrenalectomized rats. M. Herlant (1951) found some karyopyknosis in the patches of Peyer in adrenalectomized animals.

These data furthermore indicate that "stress" does not guarantee the finding of cellular disintegration in lymphoid tissues three hours or more after the induction of stress in intact animals. Diffuse reactions were found in less than 25% of the rats (ten hours after the induction of trauma), while karyopyknosis of a more localized type was found in 46% of the animals, mainly in the thymuses.

Cortisone failed to produce significant degrees of karyopyknosis in adrenalectomized rats five hours after the injection of the steroid. Some localized cellular disintegration was observed in the cortex of the thymus of one animal.

In 20% of the "Amparon"-treated animals localized karyopyknosis of some significance was found. Five rats showed these reactions in the medulla of their thymuses, and the others elsewhere. It may be of some importance that cortisone-treated and "Amparon"-treated rats show cellular disintegration in lymphoid tissues in similar percentages. There is possibly a difference between "cortisone" karyopyknosis and "Amparon" karyopyknosis, in that the latter occurs mainly in medullary areas of the lymph tissues, while the former is found in the thymus cortex. "Amparon"-treated and cortisone-treated adrenalectomized rats, unlike the untreated or adrenaline-injected adrenalectomized rats, present various degrees of thymocytic polymorphism in the medulla of the tissues studied. In this respect "Amparon"-treated animals belong in the group of rats which were in possession of genuine adrenocortical metabolites and animals which received cortisone injections.

These data suggest that the intraperitoneal administration of the enzymatically prepared casein hydrolysate "Amparon" (Organon, Holland) into adrenalectomized rats is associated with the occurrence of some increase in the rate of cellular disintegration in their lymphoid tissues, three hours after its intraperitoneal administration. The fact that these rats did not react with significant karyopyknosis after the injection of 0·9 milligramme of cortisone increases the value of the findings.

SUMMARY.

The histological features of the thymus and other lymphoid tissues of variously treated adrenalectomized rats, intact "non-stressed" and intact "stressed" rats, are discussed. It is shown that if "Amparon", an enzymatically prepared casein hydrolysate, is injected intraperitoneally into adrenalectomized rats about 20% of these animals present localized symptoms of increased rates of cellular breakdown in their lymphoid tissues and thymuses. This is not found in non-treated or adrenaline-injected adrenalectomized control rats. Cortisone induced in one out of five adrenalectomized rats karyopyknosis of a minor degree, which was also of a localized type. "Amparon" karyopyknosis and "cortisone" karyopyknosis may differ, since the former occurs mainly in medullary areas, while the latter is present in the cortex of the lymphoid tissues.

It is suggested that these findings are another indication that "Amparon" induces reactions in adrenalectomized rats which are similar in part to those observed after injections with cortisone.

ACKNOWLEDGEMENTS.

The writer is much indebted to Dr. E. B. Jones and his staff for help in this work, particularly the staining of tissues by Mr. H. C. F. Fisher.

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Reports of Cases.

CARCINOMA OF THE THYMUS.

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THYMIC CARCINOMA, although well recognized, is still sufficiently uncommon for a further case to prove of interest.

Clinical Record.

In March, 1950, three years before death, a man, aged seventy-four years, was first admitted to hospital. He complained of "heavy breathing" of three months' duration, of swelling of the left upper limb and the left side of the face for two months, and of an occasional non-productive cough. On examination of the patient the veins in the neck were seen to be engorged; the left side of the face and left arm were œdematous, and there were dilated venules over the right costal margin. Dullness to percussion was found in the second and third intercostal spaces to the left of the sternum.

Radiological examination revealed an opaque area extending out from both hilar regions, particularly on the right side. The clinical diagnosis of lymphosarcoma of the mediastinum was made, and was apparently confirmed by the radiographic disappearance of the tumour after a course of deep X-ray therapy.

Symptoms abated for more than two years, but then gradually returned, so that on his second admission to hospital in February, 1953, his dyspnœa was extreme, with audible stridor and wheezing. Engorged veins were visible in both sides of the neck, with œdema and plethora of the face, the neck and the upper limbs. Radiographic examination at this time revealed a large tumour in the upper mediastinum, a rounded shadow at the base of the left lung, and some possible collapse of the seventh thoracic vertebra, thought to be due to metastatic involvement.

He received a further course of radiotherapy, during which the leucocyte count fell from 9000 to 4000 per cubic millimetre and the number of platelets to 40,000 per cubic millimetre. His dyspnœa, which lessened during this treatment, later returned, and within his last twenty-four hours the respiratory rate rose to 60 per minute. He died in April, 1953.

Autopsy Findings.

The œdema of the head, neck and upper limbs made the upper half of his body disproportionate to the lower. Petechial spots were present on the anterior aspect of the chest and upper limbs.

There were extensive adhesions in both pleural cavities, especially at the apices and retrosternally. There was a layer of dense, hard, fibrous tissue, more than one centimetre thick, adherent to the posterior aspect of the sternum. This tissue extended laterally for a short distance behind the costal cartilages and infiltrated the upper two right intercostal spaces. Posteriorly it extended into the mediastinum to surround the superior *vena cava*, the commencement of both innominate veins and beneath and to the left of the arch of the aorta, as well as involving both hilar regions. In the fibrous tissue there were numerous small areas of necrosis and xanthochromic staining. The great veins embedded in this fibrous tissue

showed complete occlusion by thrombus, but no evidence of neoplastic invasion of the wall was to be seen with the naked eye. The fibrous tissue in the mediastinum extended into the adjacent portion of the upper lobe of the right lung.

The apex and the medial aspect of the upper lobe of the right lung were invaded by tumour, which was fusing with neoplastic deposits in the lymph nodes in the hilum and in front of the trachea. The mass so formed had a lobulated appearance (Figure I). There were a number of small islands of tumour embedded in fibrous tissue at the junction of the latter and the main tumour mass. In the lung, the tumour was sharply demarcated from the surrounding tissue and in places tended to shell out. It was cream in colour, soft, spongy and friable, with almost complete absence of fibrous tissue septa. The tumour itself was very vascular, blood flowing freely from large sinusoids on section. These numerous blood sinusoids, which were one to two centimetres long, divided the tumour into branching trabeculæ, varying from one to five millimetres in thickness.

There were small nodules of tumour present in the left lung around the hilum, and one larger metastasis about three centimetres in diameter in the left upper lobe, lying anteriorly near the interlobar fissure. This metastasis showed as a pale fluctuant swelling beneath the pleura, and, like the main tumour mass, did not impart the induration usually felt with carcinoma in the lung.

Mucopus was present in the trachea and small bronchi, and, although the right upper main bronchus was free from tumour, some of its smaller branches were somewhat compressed by it.

The pericardial cavity was obliterated by loose fibrous adhesions, and the parietal layer anteriorly was considerably thickened in its upper part by fibrous tissue infiltration. Examination of the heart showed left ventricular hypertrophy, and that of the kidneys mild nephrosclerosis with a small pelvic calculus on the right side. In the thoracic vertebræ no deformity or tumour infiltration was detected.

FIGURE I.

Tumour involving lung and hilar lymph nodes, and showing the trabeculated appearance with large blood sinusoids. There is fibrous tissue infiltration around the great vessels in the mediastinum.

Microscopic Examination.

The tumour consisted of trabeculæ of highly cellular tissue surrounding large blood sinusoids (Figure II). The individual cells showed scanty cytoplasm, and the nuclei varied in size and shape, mostly being round or oval, others more elongated. These nuclei were vesicular with thickening at the intersection of chromatin threads, while some had a distinct nucleolus. Though there were many hyperchromatic nuclei, mitotic figures were not plentiful. Giant cells with two or three nuclei, although present, were scarce. The eosinophilic cytoplasm was increased in some areas, and here the cells tended to form whorls (Figure III). The resemblance of these epidermoid whorls to Hassall's corpuscles was very striking, and occasionally in the centre there was a little calcium deposition, while in a few keratinization was seen (Figure IV). In some places the cells were more densely packed around the capillaries than elsewhere, sometimes radially and at others circumferentially.

The tumour trabeculæ contained numerous small capillaries which were lined by endothelial cells, as were the sinusoids. In some sinusoids there was old clotted blood containing cholesterol clefts.

Very little fibrous tissue was present in the tumour. There was, however, a little around a few medium-sized sinusoids, which were mainly in areas near the dense fibrosis already described. In this latter area there was

much acellular hyaline fibrous tissue, with hæmorrhages and hæmosiderin-containing macrophages. Here and there small islands of surviving tumour tissue were to be seen reproducing the highly vascular structure seen in the main tumour. Some calcification was also present in the fibrous tissue.

The superior *vena cava* was thrombosed, and organization was in progress. The tumour was not seen to extend further than the adventitia.

Lymphocytes were scanty throughout the neoplastic tissue, but were rather more frequent in the large metastasis in the left lung than elsewhere.

By silver impregnation the small capillaries showed reticulum fibres in their walls, with branching filaments spreading out for a short distance into the surrounding tissue. There was more reticulum around the medium-sized vessels, but in general it was scanty, and completely absent around the large sinusoids. In these latter sinusoids a collapsed reticulum endothelial lining was sometimes found within the lumen with blood on either side of it (Figure V).

Discussion.

As it is still not possible to be certain of the precise origin of the cellular elements of the thymus gland, a classification of the malignant tumours arising therefrom remains open to debate. For this reason they are generally grouped under the non-committal term "thymoma", which has been subdivided again into lymphosarcoma and carcinoma according to whether they are of the "small round-cell" or the "large pale-cell" type respectively. These terms are in common usage, consequently the tumour in this case has been called carcinoma. These tumours often show a fair admixture of each of the two elements, and it is for this reason that Willis (1948) considers they are all lympho-epitheliomata, with either the lymphocyte (thymocyte) or the large pale cell predominating. The tumour here reported is of interest in that the lymphocytic element was almost absent. Whether or not this was the result of irradiation it is difficult to say.

The infiltrating fibrous tissue, which is a feature of this case, is considered to be the result of irradiation of the tumour. Because the main bulk of this fibrous tissue was found in the anterior mediastinum, it is thought that the original tumour arose here. The histological features of the growth were also consistent with this opinion. Bronchogenic carcinoma was excluded because the tumour was not found to be arising from a bronchus, and, unlike bronchial carcinoma, this specimen had a sharply demarcated edge, a relative absence of fibrous tissue, a soft fluctuant consistency and a lack of characteristic induration of involved lung tissue. The large blood-filled spaces were so numerous and striking that its macroscopic appearance at the autopsy was such that the tumour was considered to be of vascular origin (Figure II).

Although thymic tumours are mostly described as being solid with numerous septa and a fibrous capsule, Willis depicts an example similar to the present one, in which there were large blood spaces.

Summary.

A case of malignant tumour of the thymus with metastases in the lung and lymph glands is described. It presented an unusual macroscopic appearance due to large blood sinuses and lack of stroma, while on microscopic examination it showed well-formed Hassall's corpuscles with keratinization in some, and a relative absence of lymphocytes.

Acknowledgements.

My thanks are due to Dr. F. Duval for his permission to publish the clinical history; to Professor F. R. Magarey and Dr. R. E. J. ten Seldam for assistance in the preparation of this article; to Mr. B. Munro for his technical skill in the preparation of the slides; and to Mr. S. Woodward-Smith, of the Department of Medical Illustration, for the photographs.

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MALIGNANT MESOTHELIOMA OF THE PLEURA.

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Clinical Record.

X., A MALE PATIENT, aged seventy-four years, was admitted to the Liverpool State Hospital on June 17, 1953, and the following history was obtained. On May 23 the patient had developed a non-productive cough associated with rather severe pain over the right side of the thorax; the pain was persistent and subject to exacerbations. It was not influenced by the phases of respiration. Two days after the onset he noticed that he was becoming breathless even at rest, and this became progressively worse up till the time of his admission to hospital. The dyspnœa was much worse when he was lying on his left side. There was no previous history of persistent cough or hæmoptysis. About four days prior to his admission to hospital he began to cough up a small amount of relatively clear sputum. He had been pyrexial over the last week and had received about ten injections of penicillin, which had reduced the temperature but had not relieved the accompanying dyspnœa. Cyanosis had never been noted, nor had there been any abdominal swelling or œdema of the ankles. His weight had always been approximately 10 stone seven pounds, but over the last week or two he had begun to lose weight. During the preceding twelve months he had noticed an increased tendency to easy bruising.

His only previous illnesses were two "attacks" of bronchitis and influenza during the winters of 1951 and 1952. There had been no dyspnœa or chest pain with these. There was no relevant family history.

On examination, the patient was seen to be a slightly emaciated old man in obvious respiratory distress. He found it impossible to inspire deeply. The signs in the chest indicated a large right-sided pleural effusion with associated displacement of the cardiac dullness to the left. There was definite tenderness over the lower right ribs. There were no signs of increased venous congestion, ascites or ankle œdema. Abdominal examination revealed no abnormality.

On June 18 right pleural aspiration under local anæsthesia yielded over two pints of dark amber fluid. It was noted that the needle had to be inserted more deeply than is customary through the eighth right intercostal space in the mid-axillary line before fluid could be obtained, and that the "resistance" offered by the chest wall was greater than usual. After the paracentesis there was still an area of dullness over the base of the right lung laterally, but it was not the stony dullness of a pleural effusion. X-ray examination revealed a diffuse opaque area at the right basal and lower zones. An ill-defined mass was seen laterally, but it could not be determined whether this was pleural or pulmonary in nature. X-ray examination on July 6 revealed recurrence of the effusion, which had coincided with a gradual redevelopment of dyspnœa.

Right pleural aspiration was repeated on July 14, and about 130 ounces of frankly blood-stained fluid were withdrawn. Some of the fluid was replaced by air, and on July 20 radiographic examination revealed a mass over the inner aspect of the fifth, sixth and seventh right ribs. There was evidence of decalcification of the lateral aspect of the seventh rib. A partial pneumothorax was present with a fluid level at the right pleural base; this revealed the tumour to be separate from lung. Small round opaque areas were to be seen throughout both lung fields, and

ILLUSTRATIONS TO THE ARTICLE BY L. A. G. HISSINK, M.D.

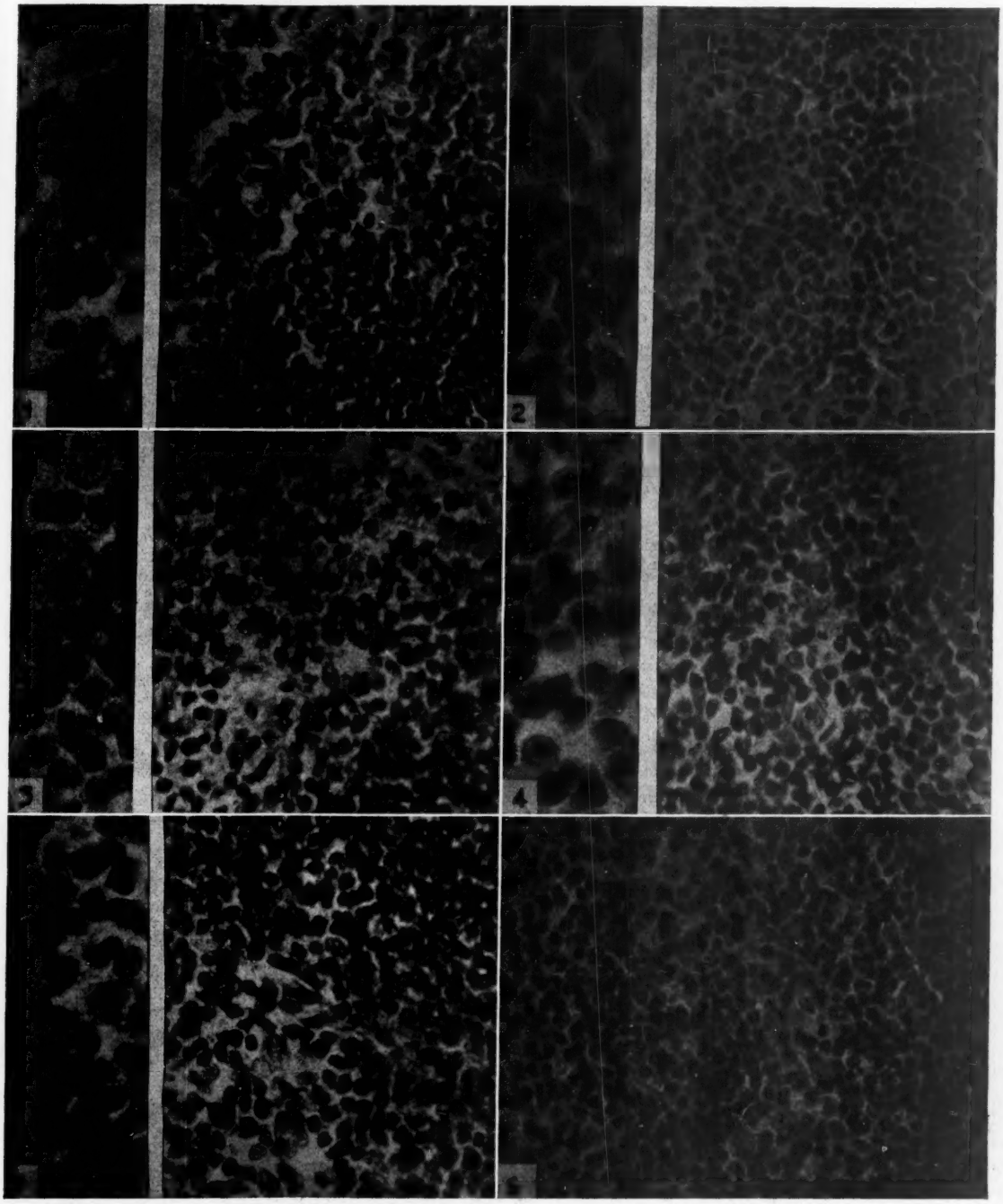

FIGURE I.—Section of thymus from intact "non-stressed" rat. (× 1000, × 450.) **FIGURE II.**—Section of thymus from intact "stressed" rat. (× 1000, × 450.) **FIGURE III.**—Section of thymus from adrenalectomized rat. (× 1000, × 450.) **FIGURE IV.**—Section of thymus from adrenalectomized rat treated with cortisone. (× 1000, × 450.) **FIGURE V.**—Section of thymus from adrenalectomized rat treated with "Amparon". (× 1000, × 450.) **FIGURE VI.**—Section of thymus from adrenalectomized rat treated with "Amparon". (× 450.)

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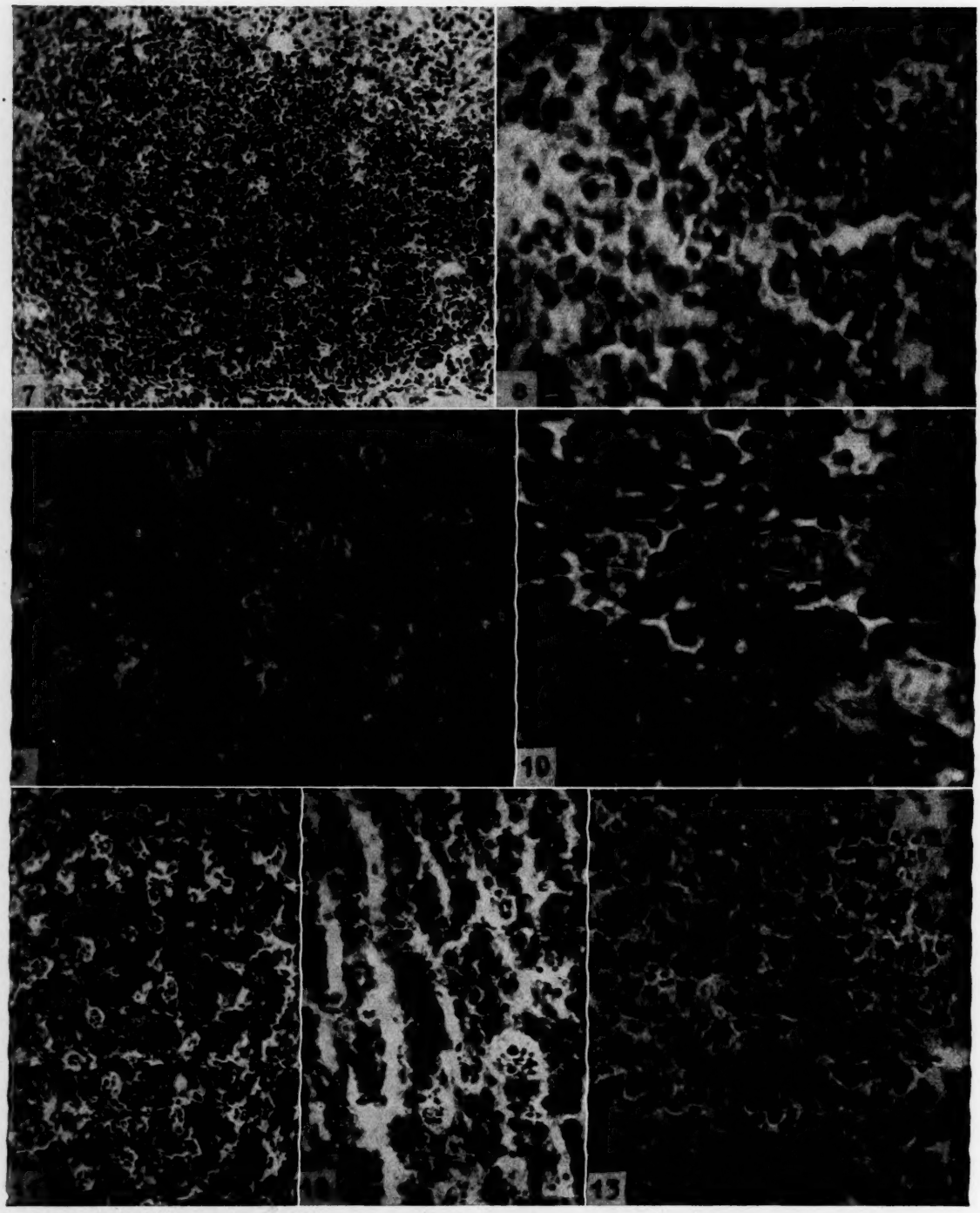

FIGURE VII.—Section of thymus from stressed intact rat—diffuse karyopyknosis. (× 100.) FIGURE VIII.—Section of thymus from stressed intact rat—localized karyopyknosis. (× 667.) FIGURE IX.—Section of lymph gland from adrenalectomized rat—karyopyknosis. (× 450.) FIGURE X.—Section of thymus from adrenalectomized rat treated with cortisone—localized karyopyknosis in cortex. (× 1000.) FIGURE XI.—Section of thymus from adrenalectomized rat treated with "Amparon"—localized karyopyknosis in medulla. (× 150.) FIGURE XII.—Section of thymus from adrenalectomized rat treated with "Amparon"—localized karyopyknosis in cortex. (× 450.) FIGURE XIII.—Section of lymphoid tissue in lung from adrenalectomized rat treated with "Amparon"—karyopyknosis. (× 600.)

ILLUSTRATIONS TO THE ARTICLE BY W. E. STEHBENS.

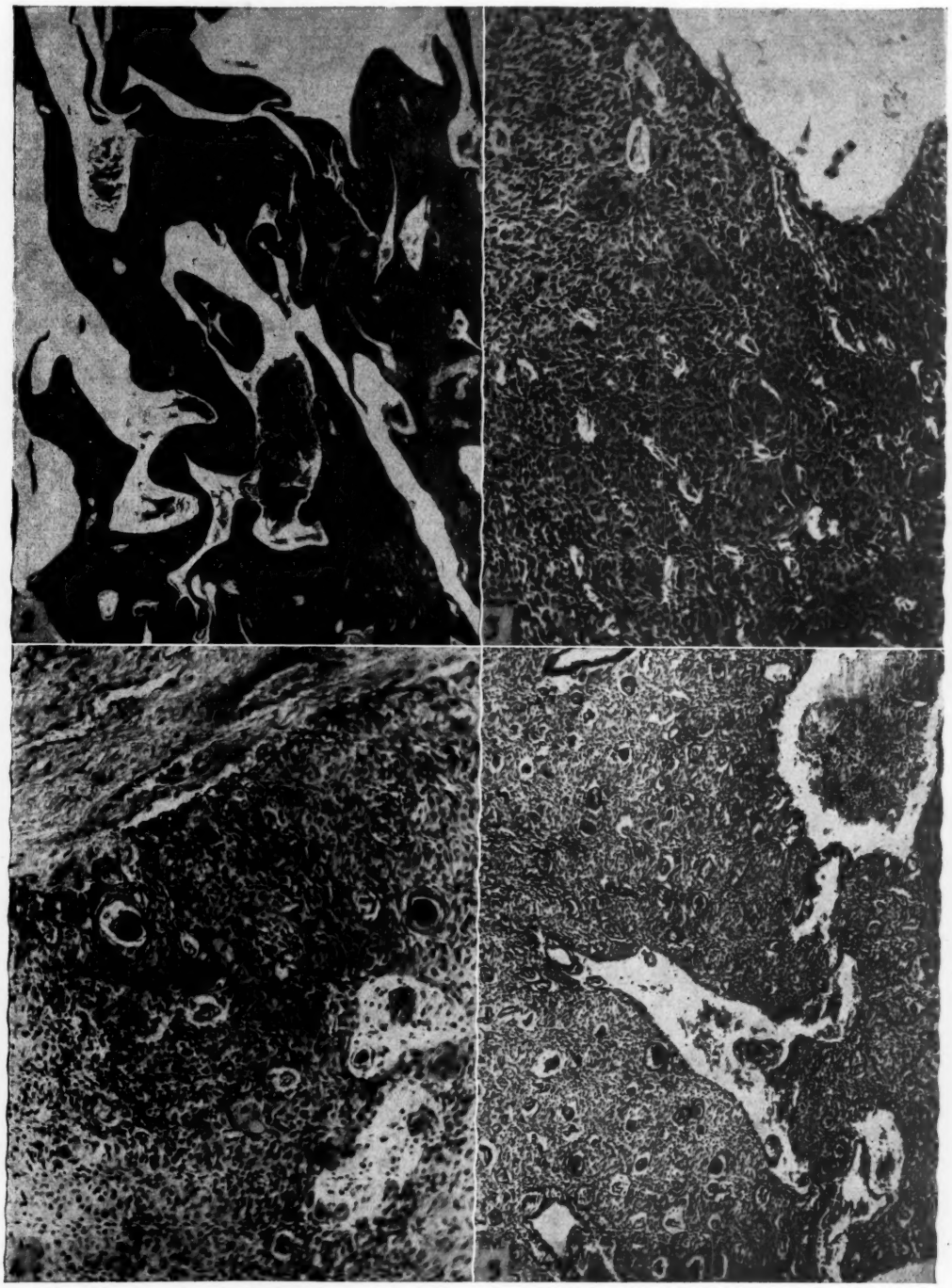

FIGURE II.—Low-power view of tumour to show the branching trabeculæ and large blood sinusoids. (Hæmatoxylin and eosin, × 12.) FIGURE III.—Cellularity and vascularity of tumour tissue are striking features. Numerous whorls resembling Hassall's corpuscles may be seen. (Hæmatoxylin and eosin, × 150.) FIGURE IV.—Keratinization present in some epidermoid whorls near the fibrous tissue. (Hæmatoxylin and eosin, × 150.) FIGURE V.—Reticulum is seen around the small capillaries, but only as collapsed circles in the large sinusoids. Blood is present on both sides of the collapsed reticulum. (Laidlaw's reticulum stain, × 75.)

ILLUSTRATIONS TO THE ARTICLE BY B. E. SHARKEY, M.B., B.S.

FIGURE I.

Left anterior oblique radiograph of the thorax, July 20, 1953, revealing an opaque area overlying the cardiac shadow. A pneumothorax is evident in the anterior aspect of the film, and a fluid level is seen inferiorly.

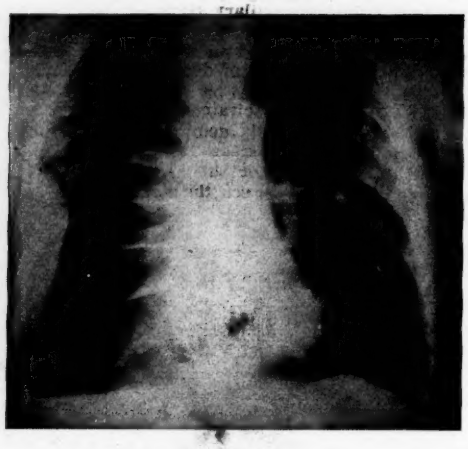

FIGURE II.

Postero-anterior radiograph of the thorax, July 27, 1953, showing: (i) a large mass in the right parietal pleura; (ii) right-sided pneumothorax with a very small amount of fluid above the right side of the diaphragm; (iii) adhesion between the upper medial aspect of the tumour and the visceral pleura; (iv) erosion of the lateral aspect of the seventh right rib; (v) secondary opaque areas throughout the lung fields.

ILLUSTRATIONS TO THE ARTICLE BY THOMAS F. ROSE.

FIGURE I.

Case I: Section of tissue removed (low power of the microscope).

FIGURE II.

Case I: Section of tissue removed (high power of the microscope).

these were considered as possible secondary deposits. After this second aspiration it was possible to percuss out an area of dullness over the lateral aspect of the right side of the thorax. This area was roughly ovoid in outline with the long axis vertical, reaching up to the fifth rib between the middle and posterior axillary lines. Over this area breath sounds and vocal resonance were diminished. A left anterior oblique film showed an opaque area coinciding with the above-mentioned area of dullness (Figure I). A third paracentesis was performed on July 22, and 20 ounces of blood-stained fluid were aspirated. X-ray examination of the thorax on July 27 fully defined the extent of the tumour (Figure II). An increase in the pneumothorax indicated, from the outline of the visceral pleura, that there was some adhesion between the upper medial aspect of the main tumour mass and a small area of the right visceral pleura. The rounded pulmonary opaque areas seemed to be more pronounced.

FIGURE III.

Post-mortem photograph showing the macroscopic appearance of the tumour *in situ*, and of secondary deposits in the right parietal pleura, and in the left visceral pleura and pericardium.

The patient was temporarily relieved after each aspiration. As his condition deteriorated, pain became more pronounced over the lower right ribs and radiated down to the epigastrium. There was considerable tenderness over the seventh rib laterally. He became progressively weaker, lost weight rapidly, and developed severe anorexia. On August 3 he began to show some vocal weakness, and on August 10 he became cyanosed. He lingered for another few days and died on August 14.

Autopsy Findings.

The body was that of an elderly man, much emaciated. There was no external deformity of the thorax. Removal of the anterior aspect of the chest wall revealed that both lungs had partially collapsed. The right pleural cavity contained about 10 ounces of grossly blood-stained fluid. A large mass, pale yellow-pink in colour and roughly ovoid in outline, measuring five inches by four and a half inches, was revealed with its long axis vertical underlying the lateral aspects of the fifth, sixth, seventh, eighth and ninth right ribs (Figure III). The mass was of smoothly nodular surface and firm consistency. In the central aspect of the tumour the seventh rib was palpably eroded for about two inches; the rib could, from the lateral surface, be felt to taper irregularly to a completely boneless area about half an inch long. Over this area of eroded and absent rib there was a softer external bulge of smooth surface one and a half inches by one inch in size, with its long axis parallel to the seventh rib. The main tumour mass was cut along the seventh intercostal space, to reveal that it was composed of yellowish-white rounded areas varying in size up to one centimetre in diameter separated from each other by thin, interlacing pinkish strands. The maximum thickness of the tumour was three centimetres, over its central point. Over a small area three-quarters of an inch in diameter, at the junction of the upper one-fifth and lower four-fifths of its medial aspect the tumour was gently adherent to and easily separated from the right visceral pleura.

Underlying the third and fourth right ribs, just above the main growth, there was a smaller, flatter tumour in the parietal pleura not attached to ribs and easily separated from overlying structures. Consistency, colour and contour were similar to those of the larger mass. Other smaller nodules were visible in the right parietal pleura.

A similar round, yellowish mass, three-quarters of an inch in diameter, was found connecting the left aspect of the pericardium with the visceral pleura over the lower lobe of the left lung, and a nodule was to be seen in the visceral pleura on the medial aspect of the left lung near its hilum. There was no evidence of metastases in the left parietal pleura.

Both lungs contained palpable, firm, rounded secondary tumours of varying size—up to half an inch in diameter; on section, these were seen to have a greyish coloration. No evidence was found of primary bronchogenic carcinoma.

Examination of the abdominal contents showed no evidence of a primary tumour, and no secondary nodules were visible.

Summary of the Histopathological Findings.

The large pleural mass was seen to be enclosed in a fibrous capsule, beneath which were areas of hæmorrhage and necrosis. The intervening tissue contained interlacing collagen bundles enclosing groups of large round or polygonal cells of epithelioid nature, which consisted of a large amount of clear cytoplasm and hyperchromatic, irregularly shaped nuclei measuring one-quarter to one-sixth of the cell diameter. The collagen bands broke the cells into cord-like columns and, in a few areas, into groups which seemed to have broken down centrally. In the deeper aspect of the tumour, the picture was of a haphazard collagen network containing cells of various shapes—spindle, polygonal, ovoid *et cetera*—with larger nuclei (half cell diameter) and finely granular eosinophilic cytoplasm. Mitoses were frequent. The deeper part of the tumour was fairly vascular.

Sections of the secondary deposits in the lungs and the pericardial metastasis corresponded with various parts of the larger tumour; but in the latter of the two was revealed a more pronounced picture of groups of cells (with a large amount of clear cytoplasm) occupying what seemed like alveolar spaces (lined by a pavement type of epithelium) and breaking down centrally to produce a lumen.

The overall appearance at first suggests that the malignant growth is arising from the cells lining the lung alveoli; but the lining cells differ morphologically from those contained in the alveoli. The consensus of opinion is that the alveolar collections of cells are probably the result of direct spread (from secondary tumour) to adjacent alveoli, and that the general appearance reveals the tumour to be a mesothelioma of the pleura with secondary neoplasia in the lungs and pleura.

Discussion.

Primary pleural tumours are rare. Cases have been reported from time to time in varying detail, but I have been able to locate only one clinical reference to this disease in Australian reports. Cotter Harvey, in 1950, quoted two cases demonstrating the two usually accepted types of primary pleural neoplasm—namely, (i) the diffuse malignant mesothelioma, and (ii) the localized malignant mesothelioma which resembles a fibrosarcoma.

The pleomorphism associated with the pathology of mesotheliomata renders classification difficult. The following is offered as a simple plan.

1. Diffuse pleural tumours. These cover large areas of parietal and visceral pleura and may form a coating for the lung. They are highly malignant.

2. Localized pleural tumours. These may be (*a*) benign or (*b*) malignant. The former include the so-called benign localized fibrous mesothelioma of the pleura first described as an entity by Stout and Murray in 1942. Fibromata, angiomata *et cetera* are extremely rare benign tumours. Malignant types may have the histological structure of a fibrosarcoma, but variegated patterns of epithelioid cells may produce differing pictures. Stout and Murray stated that no epithelioid cells were to be found in the localized type of malignant pleural tumour, and there was a tendency towards invasion of adjacent lung. The case presented does not comply with this view.

3. Mesotheliomata affecting other structures. These tumours have been reported as occurring in the peritoneum and in the pericardium. Stout, in his classification of 1950, also mentions benign mesotheliomata occurring in the male and female genital tract, but states that these have no correlation with the pleural tumours.

The diagnosis of primary pleural neoplasm is not easy to establish clinically. There are no specific symptoms or signs. The occurrence of a pleural effusion may make one more aware of its possibility, especially if the fluid is blood-stained. Examination of the pleural fluid is quite often unsatisfactory and non-diagnostic. Examination of sputum does not help. Bronchoscopic examination is of no avail except when a tumour mass arising near the hilum produces pressure effects on a large bronchus. X-ray examination may, especially after aspiration of an effusion, reveal an opaque area; but on the ordinary film one cannot be certain whether the mass is pleural or pulmonary. Diagnostic pneumothorax then becomes the only way of demonstrating the tumour as distinct from lung, although this may fail if adhesions have formed between the tumour and the lung sufficient to resist separation by a suitable pneumothorax.

The main importance attached to pleural neoplasms is the diagnosis of a benign lesion at an early stage when surgery offers the prospect of a complete cure. Unfortunately the case reported above did not fall into this category.

Summary.

This case is proffered as one of primary localized pleural neoplasm presenting as a pleural effusion, metastasizing to lung and pleura, and revealed histologically to be a malignant mesothelioma.

Acknowledgements.

My thanks are due to Dr. V. J. McGovern, of the Fairfax Institute of Pathology, Royal Prince Alfred Hospital, Sydney, for the preparation of the microscopic slides and for his helpful comments; also to Dr. F. R. Magarey, Professor of Pathology, University of Sydney, and Dr. R. ten Seldam, of the Department of Pathology, University of Sydney, for their opinions as to the nature of the tumour.

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DIFFICULTIES IN THE DIAGNOSIS OF BREAST CARCINOMA IN THE PRESENCE OF LARGE BREAST CYSTS.

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LARGE breast cysts, one of the manifestations of hyperplastic cystic disease of the breast, may cause difficulties in the diagnosis of breast carcinoma in two ways. Firstly, neoplastic changes may occur in their walls (Cases I and II), and secondly, a large cyst or group of cysts may hide an underlying neoplasm (Cases III, IV and V).

Carcinoma Arising in the Wall of a Breast Cyst.

Case I.

The patient was a married woman, aged thirty-four years, with two children, aged three and five years respectively. For two months she had noticed in the left breast a swelling which fluctuated in size, becoming larger and tender at the commencement of her menses.

Examination of the patient revealed a firm, rounded, slightly tender swelling in the upper outer quadrant of the left breast, about an inch from the nipple. It was smooth and not attached to the skin or deeper structures. There was no nipple retraction or discharge. There were no other swellings in that breast, and the regional lymph nodes were not enlarged. The right breast was normal. The diagnosis was that of a simple breast cyst.

At operation the swelling was removed with a small area of surrounding breast tissue. Two centimetres in diameter, it was a smooth-walled, unilocular cyst full of clear fluid. Though macroscopically simple, the report on the microscopic examination was as follows (Figures I and II):

> This cyst is lined by pseudostratified epithelium which in places has desquamated from the fibrous wall surrounding the cyst. In many places the cells from the deeper layers of the epithelium are invading the fibrous tissue wall, suggesting that the epithelium has undergone malignant changes. The cytological appearances of the cells, prominent nucleoli, hyperchromatic nuclei, numerous mitotic figures, are those of carcinoma cells.

The diagnosis was therefore that of a pseudostratified (squamoid) carcinoma arising in a solitary breast cyst.

As the patient refused further operation, a course of deep X-ray therapy was given. A three-year follow-up so far has shown no evidence of recurrence.

Case II.

This patient, a married woman, aged forty-two years, had two sons, aged twelve and eighteen years respectively. For five months she had noticed a swelling in the right breast. It was gradually increasing in size and was painful at the menses.

Examination of the patient disclosed a large, smooth, round, freely mobile swelling just above the nipple of the right breast. There was no attachment to skin or fascia, and no enlarged lymph nodes were present. Both breasts had the shotty feel of generalized hyperplastic cystic disease. It was considered that one of these little cysts had outgrown its fellows.

At operation, the segment containing the cyst was removed and the specimen examined. There was found a cyst, three centimetres in diameter, in the centre of the specimen, which was the seat of generalized cystic disease. Full of clear fluid, the cyst was smooth-walled except in one part, where a hard, wart-like mass projected both into the lumen and outwards into the pericystic tissues. This mural nodule was examined microscopically and found to be an adenocarcinoma of a high degree of malignancy. Consequently, six days later a radical mastectomy was performed. Examination of the specimen disclosed no involvement of the axillary lymph nodes.

Comment.

Though Patey (1953) has shown that cystic disease of the breast, especially in the form of a solitary cyst in one breast, is essentially a benign condition, nevertheless carcinoma does arise occasionally in the cyst walls, as in the above-mentioned cases.

Both patients were diagnosed as having simple cysts and the carcinoma was quite unsuspected until operation was performed.

Both these cysts were full of clear fluid, so that aspiration would have been useless in the diagnosis of the carcinoma unless some tumour cells had been found in the fluid. Even had these cysts been aspirated before operation, palpation would not have revealed the growths, as they were too small to feel.

Consequently, these two examples show the fallacies of aspiration both in the diagnosis and in the treatment of breast cysts. These cysts must be explored and excised together with the segment of the breast in which they arise, so that the surrounding breast tissue can be examined as well. This is essential, as may be seen in the following cases, in which the neoplasms were shielded from the palpating fingers by large cysts.

Breast Cysts Hiding an Underlying Carcinoma.

Case III.

This patient, a single woman, aged forty-seven years, had noticed a swelling in the left breast for seven months. It had appeared almost overnight and then gradually decreased in size over the first four months, so that when she was then examined by her doctor a small, smooth cyst only was palpable. However, a second cystic swelling then appeared close to the first, and they both increased rapidly in size during the next three months.

Examination of the patient disclosed two cystic swellings in the lower inner quadrant of the left breast. They were smooth, rounded and freely movable. Though no neoplasm was palpable in this breast, a hard enlarged lymph node was felt in the left axilla. Both breasts had the shotty feel of hyperplastic cystic disease.

Operation was performed and the affected breast segment removed. In it were several large, smooth-walled cysts full of clear fluid. Deep to them and lying in between several smaller cysts was a small area of obvious scirrhous carcinoma. Radical mastectomy was thereupon performed.

Examination of the rest of the breast disclosed generalized cystic disease, though there were no more large cysts. There were three enlarged lymph nodes in the axillary tissue. Microscopic examination disclosed that the neoplasm was a scirrhous carcinoma, and the three lymph nodes were heavily invaded.

Case IV.

This patient was a married woman, aged forty-one years, with no children. She had had painful swellings below the nipple of the left breast for six months. These swellings fluctuated in size, being most painful when large. This fluctuation in size and intensity of pain had no relation to the menses.

Examination of the patient disclosed in both breasts the shotty feel of hyperplastic cystic disease. Beneath the nipple of the left breast there were several smooth rounded swellings which felt elastic in consistency. No enlarged axillary lymph nodes were palpable.

The left breast was explored and the segment containing the larger swellings removed. Inspection of the specimen disclosed several large, smooth-walled cysts full of clear fluid. In between these cysts was a small, hard area typical of a scirrhous carcinoma. Radical mastectomy was immediately performed.

Examination of the rest of the breast disclosed hyperplastic cystic disease. There were two enlarged lymph nodes in the axillary tissue. The neoplasm was found on microscopic examination to be a scirrhous carcinoma, and the enlarged lymph nodes were similarly involved.

Case V.

This patient was a married woman, aged fifty-three years, with two adult daughters.

Eighteen years previously the patient's left breast had been amputated for cystic disease. At that time she had noticed a small, painless swelling in the right breast lateral to the nipple. She was told that this was a cyst and that it did not require removal. It grew very slowly over the next seventeen and a half years, but in the following six months it increased rapidly in size and became painful.

Examination of the patient disclosed a firm, smooth rounded swelling lateral to the right nipple. It was unattached to the skin or to deeper structures. The rest of the breast appeared normal. One small, hard lymph node was palpable in the right axilla. The left breast had been removed by simple mastectomy.

At operation, the affected segment of the right breast was removed. It was found to consist of a mass of cysts of varying size set in fibrous tissue like stroma. These cysts were full of clear fluid. One area felt much harder than the rest and looked like a scirrhous carcinoma. Examination of frozen sections confirmed this, and a right

radical mastectomy was performed. The rest of the breast was found to be the seat of generalized hyperplastic cystic disease. Two lymph nodes were found in the axillary tissue to be full of carcinoma cells.

Comment.

All these patients (Cases III, IV and V) had generalized hyperplastic cystic disease of the breasts. However, in each instance the cysts around the carcinoma were much larger than elsewhere in the breast. In Cases III and IV these had become apparent to the patient only in the few months before consultation. In Case V a swelling known to have altered little in size over seventeen and a half years suddenly became larger over the next six months. It may well be that the presence of carcinoma acts as a stimulus to the increased growth of any nearby cyst. Consequently any swelling, diagnosed as a breast cyst, which starts to increase quickly in size must be regarded with suspicion. It may be the herald of an adjacent unsuspected malignant growth. In any case, these cysts successfully hid the underlying malignant growth from the palpating finger, so that in each instance the patient had been reassured that the mass was only a harmless cyst, until in Cases III and V the appearance of enlarged axillary lymph nodes showed that something graver was afoot.

Thus, one must again emphasize the importance of exploring all cystic swellings of the breast rather than temporizing with aspiration.

Summary.

Two cases of carcinoma arising in the wall of a large breast cyst are discussed. Three cases of large breast cysts successfully hiding early carcinoma from the palpating finger are also reported.

It is pointed out that in each instance the cysts concerned were full of clear fluid, so that aspiration would not have helped in the diagnosis of malignant disease. Even had the cysts been caused to collapse by aspiration of their contents, the neoplasms could not have been palpated because of the smallness of their size and the numerous other small cysts around them.

Consequently, any breast swelling, no matter how innocent it may seem, should be examined at operation as in the cases here reported.

Acknowledgements.

I wish to thank Dr. Colin Graham, morbid anatomist at the Royal North Shore Hospital, for examining the sections in Cases I and V. I wish also to thank Miss M. Simpson, of the Photography Department of the Unit of Clinical Investigation, for the photomicrographs.

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THE BONNEVIE-ULLRICH SYNDROME.

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TURNER (1938) described the triad of infantilism, *pterygium colli* (webbed neck) and *cubitus valgus*. Growth in height is stunted and there is increased urinary excretion of gonadotrophin after puberty (urinary gonadotrophin excretion is very small before puberty). In addition, there are frequently a lowered hair-line on the neck, ear deformities, coarctation of the aorta and scoliosis. Intelligence is usually normal. Turner's original ten cases occurred in females, aged fifteen to twenty-three years. Cunningham and Harley (1951) and Dorff *et alii* (1948) reported cases of Turner's syndrome in males.

The Bonnevie-Ullrich syndrome, in addition to *pterygium colli*, is especially characterized by lymphangiectatic œdema, retardation of growth, skeletal anomalies, dystrophy of nails *et cetera*.

Kristine Bonnevie (1934) postulated that *pterygium colli* and the associated anomalies could be produced by raising inbred Bagg-Little mice (Bagg and Little, 1924) and exposing them to X rays whilst in embryo. According to Bonnevie, the malformations were the result of an extrusion of excess quantity of liquor through the occipital gap in the fourth ventricle, causing migratory myelencephalic blebs.

FIGURE I.
Showing *pterygium colli* (webbed neck).

Ullrich (1938), carrying out further investigations, confirmed Bonnevie's original thesis and inferred that the process causing the multiple malformations in Bagg-Little mice offered an illuminating explanation of a very similar combination of deformities in man.

However, Ullrich (1949) modified his original concept, and concluded that, in view of the consistent symmetrical distribution of all the defects, the Bonnevie-Ullrich syndrome was incompatible with the wandering bleb mechanism.

Clinical Record.

"S.", a girl, aged thirteen months, was first examined on March 13, 1953. Her birth weight was 3·2 kilograms. Apart from one mild attack of bronchitis, she had had no previous illness. Both parents were alive and well. There was considerable sexual disharmony between the parents. There were three other siblings, aged six, four and three years respectively, who were all well. The family background was non-contributory. The mother developed mumps when three and a half months pregnant.

On examination of the child, the temperature, respiration and pulse were normal, as were the heart, lungs, abdomen and central nervous system. The head circumference was 43 centimetres, the weight was 10·45 kilograms and the length was 69·8 centimetres. The general appearance was that of a sallow infant with sagging eyelids (no actual ptosis was present) and deep-set corners of the mouth, giving the appearance of the peculiar characteristic

triangle-shaped mouth described as "wolf jaw". She had *pterygium colli* (Figure I) and congenital lymphangiectatic œdema of the hands and feet (Figures II and III). The right ear was larger than the left. The hair-line of her neck was low. Pronounced scoliosis, funnel chest and dystrophy of her hands and feet were present. Her mental development appeared normal.

A number of investigations were carried out. A blood examination revealed that the hæmoglobin value was 10·7 grammes *per centum* and the white cells numbered 9000 per cubic millimetre; the mean corpuscular diameter was 7·0μ. A differential leucocyte count revealed a lymphocytosis of 50%, but no other abnormality. Microscopic examination of the urine revealed no abnormality. The serum calcium content was 10 milligrammes *per centum*, the serum alkaline phosphatase content was six units, the serum cholesterol content was 320 milligrammes *per centum*, and the plasma chloride content was 370 milligrammes per 100 millilitres. There was no reaction to the tuberculin test, and no phenylpyruvic acid was detected in the urine. The Kline test produced a negative result.

FIGURE II.
Infant, aged three days; well-marked congenital lymphangiectatic œdema.

X-ray examination revealed fusion of the seventh and eighth ribs on the right side and hemivertebræ in the eighth dorsal vertebra. There was no evidence of Klippel-Feil syndrome, Sprengel's deformity or Pott's disease.

Discussion.

This patient shows the classical signs of the Bonnevie-Ullrich syndrome—webbed neck, congenital lymphangiectatic œdema, low neck hair-line, dystrophy of the nails, and the characteristic physiognomy and various skeletal defects.

It is clear that the Bonnevie-Ullrich syndrome is intimately related to such conditions as Turner's syndrome and Nielsen's *dystrophia brevicollis congenita*, recognized by Klippel-Feil syndrome, *pterygium colli* and anomalies of the hair-line of the neck.

It is difficult to apply Kristine Bonnevie's theory to all the manifestations of this syndrome, and Ullrich now admits that the symmetrical distribution of the defects is incompatible with the wandering bleb mechanism.

Turner maintained that the syndrome he described was due to ovarian agenesis, but complete agenesis of the ovaries is not always present and Turner's syndrome is reported in the male. Certainly, in many cases there are signs of infantilism and hypogonadism. Endocrine disorders can therefore be of only secondary significance in the pathogenesis of Turner's syndrome as a whole.

FIGURE III.
Infant, aged three days; webbed neck and congenital lymphangiectatic œdema of hand.

It is of interest to note that, in the present case, the mother developed mumps when three and a half months pregnant. Epididymo-orchitis and ovaritis are common complications of epidemic parotitis after puberty, and, though unusual, complications before puberty nevertheless do occur. Occasionally the thyroid, thymus and breasts are involved. The Bonnevie-Ullrich syndrome is accompanied by infantilism. Turner's syndrome, though much more frequent in the female, also occurs in the male. I can only postulate that there may be some significant ætiological relationship between the occurrence of mumps in the mother during the third month of pregnancy and the development of the Bonnevie-Ullrich syndrome.

Summary.

A case is reported presenting the classical picture of Bonnevie-Ullrich syndrome. Comment is made on the close similarity between this syndrome and Turner's syndrome. References are made to the literature relating to the pathogenesis, none of which gives a satisfactory ætiological reason for all the manifestations. Attention is drawn to the mother's developing mumps when three and a half months pregnant, and consideration is given to the possibility whether this occurrence has any relationship to the pathogenesis.

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Reviews.

Emotional Factors in Skin Disease. By Eric Wittkower, M.D., and Brian Russell, M.D., with contributions from Peter Edgell, Desmond Irwin and John Siorach, and forewords by Dr. R. M. B. MacKenna and Professor D. E. Cameron; 1953. New York: Paul B. Hoeber, Incorporated. A Psychosomatic Medicine Monograph. 9½" × 6½", pp. 224. Price: $4.00.

THIS book is a psychosomatic medicine monograph by two able clinicians, a dermatologist and a psychiatrist. It includes forewords by Dr. R. M. B. MacKenna (London) and Professor D. E. Cameron (Montreal). There are two parts to the text and the end of each chapter carries a summary and conclusions relating to the principal features of the chapter. Part I deals with the psychosomatic approach to skin diseases, with the anatomy and physiology of the skin and with the investigation and management of skin disorders. Part II deals with specific conditions, referring to abnormal skin sensations and abnormal skin manifestations.

We agree wholeheartedly with the authors that "reluctance to admit the relevance of emotional factors [in dermatology] is marked in some quarters". This reluctance does not admit that mind and body are inseparable. However, granting acceptance of the principle of unity of psyche and soma, the authors' attempts to draw ætiological conclusions from this principle are not always convincing and are often obscured by wordiness.

The case histories are of great interest, and in themselves seem more instructive than much of the text, which stresses the obvious more than is necessary; for example, " . . . if the patient starts to weep, blush, or sweat on mentioning any particular topic, or quietly dismisses the subject as of no importance, or starts scratching the affected skin, then the examiner can be satisfied that the patient is touched to the quick, in a psychological as well as in a dermatological sense".

It is agreed that most dermatologists can cope with the more superficial problems in the psychiatric approach to skin diseases and that they can give the patient insight and some emotional relief. The deeper problems call for psychiatric assistance.

The skin conditions discussed include *pruritus vulvæ*, *pruritus ani*, eczema, pompholyx, psoriasis, seborrhœic dermatitis, urticaria, rosacea, acne and alopecia. The final chapter deals with the skin and psychoses. In this chapter 223 cases of skin disease among 13,468 psychotic patients are classified. Although the conclusions are interesting they are not very informative.

The book is well edited on the whole, although the title on the cover differs by one letter from that on the front page. We recommend the book to all practitioners interested in psychosomatic medicine and think that its publication will help to overcome some of the reluctance previously mentioned.

Diuretic Therapy: The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. By Alfred Vogl, M.D.; 1953. Baltimore: The Williams and Wilkins Company. London: Baillière, Tindall and Cox. Sydney: Angus and Robertson, Limited. 9" × 6½", pp. 262, with five text figures. Price: 53s. 9d.

ALFRED VOGL, the first physician to observe the diuretic effect of an organic mercurial compound on a patient receiving treatment for syphilis, has produced a comprehensive monograph on diuretic therapy. An introductory chapter on the pathogenesis of œdema is followed by a review of the indications for diuretic therapy. While the use of diuretics in congestive cardiac failure is the main subject, attention is paid to the treatment of œdema in hepatic cirrhosis with ascites, nephritic and nephrotic œdema, beriberi heart disease, chronic post-phlebitic œdema and other conditions. The pharmacology and clinical usefulness of the more important diuretic drugs are briefly discussed, most attention being paid to the organic mercurial diuretics, including the newer forms for subcutaneous and oral use.

The author points out that the practice of diuretic therapy is wider than the mere use of diuretic drugs. The value of rest, the diet with the low sodium content, the care necessary in maintaining electrolyte balance, the use of the cation exchange resins and the mechanical removal of fluid all play their part. It is emphasized that, in the treatment of congestive cardiac failure, mercurial diuretics supplement but do not replace bed rest, adequate digitalization and salt restriction. Diuretic drugs should be ordered as individual doses, depending on the response of the patient, not as a "routine course" of injections. Practical advice is given on dosage and the use of diuretic adjuvants such as acidifying salts. Side effects—toxic reactions or hypersensitivity to mercury—and the effects of excessive diuresis are clearly discussed, including the differential diagnosis and management of complications caused by excessive diuresis. The absolute contraindications to the use of mercurial diuretics are given. In other conditions traditionally regarded as contraindications the judicious use of mercurials may as a rule be safely undertaken. The management of refractory œdema and the combination of diuretic drugs is well covered, with some illustrative case commentaries.

There is also brief reference to antidiuretic substances such as sodium compounds and various narcotics, sedatives and analgesics (including "Butazolidin"), nicotine and adrenal corticoids which can counteract or neutralize the effect of the diuretics.

An extensive bibliography is given. Altogether this short book is practical, easily read and of the greatest value to all practitioners undertaking the care of medical cases.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Favourite Prescriptions", edited by Heneage Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S., and William A. R. Thomson, M.D.; Second Edition; 1954. London: The Practitioner. 9" × 6", pp. 88. Price: 5s.

There are eleven authors to this volume.

"Practical Clinical Biochemistry", by Harold Varley, M.Sc., F.R.I.C.; 1954. London: William Heinemann (Medical Books), Limited. 9" × 6", pp. 558, with 70 text figures. Price: 42s.

A survey of the whole subject and intended specially for registrars training in clinical pathology, hospital biochemists and laboratory technicians.

"Nerve Impulse: Transactions of the Fourth Conference, March 4, 5 and 6, 1953, Princeton, N.J.", edited by David Nachmansohn, M.D.; 1954. New York: Josiah Macy Junior Foundation. 9" × 6½", pp. 224, with 54 illustrations. Price: $4.00.

The subjects discussed were the mechanism of vision, the mechanism of hearing and sensory receptors.

The Medical Journal of Australia

SATURDAY, MAY 8, 1954.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

PROGNOSIS IN HEART DISEASE.

IN 1913 James Mackenzie wrote in the third edition of his book "Diseases of the Heart": "I am rather afraid that our profession as a body does not recognize sufficiently its responsibility in regard to prognosis. When an individual submits himself for an opinion he does so with such implicit confidence that the verdict given may alter the whole tenor of his life. . . . A serious responsibility is thrown upon every practitioner at times in advising upon certain questions." Forty years later Paul D. White[1] can quote this statement, and still be obliged to say that prognosis remains "a stepchild in medical advance partly because it is a difficult subject and partly because, for some reason or other, it has rarely been studied scientifically". He feels sure that the doctor today can do better than he has in the past, and points firstly to the greater amount of knowledge available on which to base prognosis, and secondly to the need to call more on the laws of chance. In a thoughtful attempt to organize the application of available scientific knowledge, White presents ten factors that combine to form the basis for cardio-vascular prognosis in any given case. The first factor, which is described as "very basic", is heredity. There seems little question that the patient with long-lived ancestors or near relatives is likely, other things being equal, to live longer than the patient with short-lived ancestors or near relatives, and in general this principle is quite relevant to the prognosis in cardio-vascular conditions. There is some suggestion that in relation to coronary disease the maternal inheritance is more potent than the paternal. White points out that in practice it is of great importance for the physician to inquire specifically about the ages and causes of death or important illnesses in parents and siblings, and even on occasions in grandparents, uncles, aunts and children. This procedure should be routine in cases of cardio-vascular disease. However, this factor does not stand alone, and an unfavourable family history should not be allowed to depress any particular patient. The second and third factors are age and sex. Other things again being equal, the older the patient after the period of infancy, the worse the prognosis. It must be realized, however, that chronological age is not the same as physical age. The sex factor is seen in the fact that, yet again other things being equal, men are more vulnerable and have an earlier and higher mortality than women in most cardio-vascular conditions. Coronary heart disease is a condition of middle-aged men, and in White's experience the prognosis has been somewhat worse than in women. The fourth factor, the type of heart disease, is, of course, of paramount importance; but the picture here is changing. Modern methods of treatment have greatly modified the gloomy prognosis that was formerly inevitable in two particular conditions—namely, subacute bacterial endocarditis and syphilitic aortitis. The position is also much brighter for many patients with congenital defects of the heart and great blood vessels, although many baffling problems remain. It would seem that in these cases a prognosis should not be given until the patient has had the benefit of the advice of those particularly well informed and skilled in this field. Another prognosis that used to be very bad, that of the patient with the thyrotoxic heart, has also improved greatly, not only because of better treatment when the condition has become established, but also because of the early recognition and cure of thyrotoxicosis before the heart becomes seriously involved. By contrast with these conditions, White refers to three types of heart disease that continue to challenge us, and for which we can as yet do little to better the prognosis. The first of these is *cor pulmonale*, both the chronic and the acute types. In this condition, by the time the heart is seriously affected with dilatation and failure of the right ventricle, the prognosis is very grave and life hangs in the balance. Hypertensive cardio-vascular disease presents a grimmer problem because of its great prevalence and our failure to discover adequate specific therapy. In many cases the condition is mild and the prognosis is good for many years; but even in some of these cases the condition becomes malignant, and we cannot always prophesy which these will be. White points out that in the study of patients with hypertension, it is necessary to gather together all known factors on which to base a reasonable individual prognosis. It is also of interest to try to determine when possible where the greatest threat lies—on the heart, on the cerebral circulation or on the kidneys. A very high diastolic pressure in a young or middle-aged man is an immediate threat to the heart; commencing abnormalities of urine and renal function point to serious kidney disease; and so-called hypertensive encephalopathy, especially with "little strokes", favours termination of life by a cerebral vascular accident. The most difficult problem in cardiac prognosis, according to White, is that associated with *angina pectoris*. He points out that despite considerable advances in the understanding of this condition during the last twenty-five years, it is still considered wise to "guard" the prognosis in almost every case. His view is that we should be able

[1] *J.A.M.A.*, September 12, 1953.

to do better than this; but it requires a lot more study of the factors concerned and their careful application to the individual patient.

Another of the ten factors described as of prognostic importance at least equal to the kind of heart disease, is the degree of severity of that disease. With two coexisting conditions it is usually better to base the prognosis on the severe lesion, and not alter it much on the finding of a lesser lesion. White has not found one abnormality compensating for another, as is sometimes described as happening; his experience is rather that various lesions are additive in their prognostic significance. He states that one of the most important clues to help in estimating the degree of heart disease is the size of the heart; in general, the larger the heart, the worse the prognosis. The sixth factor is the stage of the disease. Generally speaking, the earlier the stage, the less severe the condition and the better the immediate prognosis with adequate treatment. An apparent exception to this is massive myocardial infarction, which offers the greatest threat to life during the first hour or two; but even here, the earlier adequate treatment can be applied, the better the prognosis. This brings us to the next factor, the adequacy of treatment, which is rather obvious but important. As White states, even the most ignorant physician is supplied with therapeutic tools that permit him to prolong lives that would have been lost a generation or two ago. The eighth factor is rather elusive, but cannot be put aside. It is simply the great annual increase of medical knowledge resulting largely from research. It has to be borne in mind all the time that round the corner there may be a cure, or at least some improvement of a current therapeutic measure, that may radically alter the prognosis. Encouragement to look for these possibilities is provided by what has been achieved recently in the management of subacute bacterial endocarditis and congenital heart disease. Another vital factor that the medical adviser should be at pains to assess is the degree of cooperation of the patient. The difference between life and death may easily depend on this factor. That is why, as White points out, it is essential for the physician to establish at the very beginning a good relationship, and to take time to explain as fully as is necessary what is wrong and what should be done without going into tedious detail or recounting all the bad complications that could develop. An hour spent in this way may save weeks and months of miserable apprehension and unhappy rebellion. The last factor is the attitude of all concerned, including the physician, the patient, his family and friends, and even on occasion the community. Optimism can play a significant role in improving the prognosis, although it can be overdone and should not be allowed when there is no possible justification for it. Over-confidence and carelessness on the part of physician and patient may lead to unfortunate results; but at least the old adage of "while there is life there is hope" proves true often enough, even in the sickest patient, to justify its use without over-confidence. White agrees, at the conclusion of his paper, that assessment of the relative values of the various factors that he has mentioned is extremely difficult, and in fact practically impossible in the present state of our knowledge or of our ignorance. Nevertheless a start must be made in relation to the individual patient, and with deliberate effort in this direction and growing experience it should be possible for the art of making a prognosis to become a science.

Current Comment.

ADRENAL SURGERY.

THE once forbidding problems involved in adrenal surgery have taken on a new aspect in the light of our present knowledge of adrenal physiology and steroid chemistry. Bilateral total adrenalectomy, without replacement therapy, leads to death within ten days, and Addison's disease used to be considered an invariably fatal condition. With the synthesis and use of DOCA (desoxycorticosterone acetate) the outlook was changed, as J. W. Jailer[1] has pointed out, but it is now known that this steroid alone is not sufficient for complete adrenocortical replacement. Adrenal cortical extract has had to be used to supplement DOCA, and it is only since the introduction of cortisone that radical adrenal surgery has been possible with a reasonably small risk. Jailer goes on to state that desoxycorticosterone, as the term "desoxy" implies, lacks an oxygen atom at the eleventh carbon atom. Its effect is primarily on salt and water metabolism, being but little on protein and carbohydrate metabolism. DOCA can maintain life in the adrenalectomized animal, but cannot protect against a stress like cold, infections or toxins. The 11-oxysteroids, on the other hand, as represented by cortisone (compound F), are more effective against stress. They have an effect on protein metabolism and gluconeogenesis and increase the capacity of muscles for work. One of their important effects is to suppress ACTH production by the pituitary. The other hormone at our disposal is ACTH; its effects are mediated through the adrenal, and it is ineffective in the absence of the adrenal cortex.

In an overall review of pre-operative and post-operative care in adrenal surgery, Jailer refers first to the performance of total adrenalectomy for malignant hypertension, prostatic carcinoma and mammary carcinoma. He states that if the adrenalectomy is performed in two stages, no special preparation is necessary for the first stage. Otherwise the patient is given 200 milligrammes of cortisone intramuscularly on the day before operation. On the day of operation 200 milligrammes of cortisone *plus* five milligrammes of DOCA are given. The next day these two substances are given again (in the same dose). After that, cortisone administration is gradually tapered off. Adrenalectomy is also performed for Cushing's syndrome. It has not been established whether the syndrome is due primarily to pituitary or primarily to adrenal cortical disease. However, there is no doubt that the clinical manifestations are due to excessive corticoid secretion. If an adrenal tumour exists in the presence of this clinical entity, the opposite adrenal is invariably atrophic. In other words, if no replacement therapy is used in conjunction with the removal of the diseased adrenal, the operation is tantamount to bilateral total adrenalectomy. The rationale of therapy is therefore replacement with cortisone and DOCA, as well as ACTH, to stimulate the function of the atrophic contralateral gland. If, in the immediate post-operative period, the blood pressure falls, infusions of nor-adrenaline or "Neo-Synephrine" and blood should be given. Serum sodium and potassium levels are carefully followed, and these electrolytes are replaced, if necessary. When Cushing's syndrome is due to bilateral adrenal hyperplasia, as it mostly is, the usual routine is to remove 90% of one adrenal and at a future date to remove the opposite gland completely. The replacement therapy is similar to that outlined for bilateral adrenalectomy in malignant hypertension. The adrenogenital syndrome, or adrenal virilism, may be due to adrenal hyper-

[1] *J. Urol.*, August, 1953.

plasia or neoplasm. Owing to the differences in the steroids elaborated in this condition compared with those of Cushing's syndrome, the metabolic alterations are different, and so is the operative procedure. Very little or no hormonal support is necessary. Jailer, being a physician, describes "medical adrenalectomy" as follows: ACTH stimulates the adrenal cortex, and conversely cortisone (compound F) inhibits the pituitary from secreting more ACTH; thus, in patients with adrenal virilism due to bilateral adrenal hyperplasia, the administration of cortisone results in an indirect decrease of adrenal secretion, and at the same time the substitution of a more normal adrenal steroid for the abnormal ones being established in this syndrome.

CARBOHYDRATE IN THE TREATMENT OF DIABETIC KETOSIS.

THERE has been considerable argument concerning the value of carbohydrate, given in addition to insulin, in the treatment of ketosis occurring in the human subject with diabetes. It has been pointed out that examinations for urinary ketones, particularly if qualitative methods are used, are not a trustworthy guide to the degree of ketonæmia. M. Rosecan and W. H. Daughaday, in a study on this subject, state that one reason for this is that ketones continue to be excreted in the urine until the level in the blood is very low, and at this stage may appear in the urine in a concentration which still gives a reaction in a qualitative test.[1] These authors have carried out an investigation based on the study of eight diabetics, in whom a state of ketosis had been induced, using the ketone blood level as the criterion of the ketosis. The subjects of the experiment were five women and three men, in age ranging from nineteen to sixty-seven years, and otherwise healthy. Insulin was withheld for one to three days, and the blood ketone levels were studied. The authors found that dehydration did not occur in spite of well marked polyuria. Clinical signs of ketosis were not observed, except that two patients vomited slightly and one had Kussmaul respirations. An attempt was made to achieve equivalent degrees of ketosis in each individual patient, and insulin dosage was likewise kept constant for each patient. A 10% solution of glucose or fructose was given intravenously at a standard rate for four hours, and control patients were used who received insulin and infusions of saline solution. Though routines differed somewhat with different patients, all infusions were given early in the morning, usually fourteen hours after the last meal. Standard methods of analysis were used for the biochemical determinations. The carbohydrate infusions maintained a rate of 0·8 gramme per kilogram per hour. An average dose of 45 units of insulin was needed to reduce the blood sugar to normal limits in the controls. Study of the tables and graphs is, of course, necessary for a clear presentation of the results, but the authors summarize their findings in the behaviour of the carbohydrate component of the patients' intake as follows. When carbohydrate was given the rapid drop in blood ketones might be due to three processes. These were the increased excretion from the kidneys, the increased peripheral utilization of the ketones and the decreased production of ketones by the liver. The first of these possibilities the authors eliminate because the total ketonuria remained constant in the different therapeutic procedures. The second possible factor is not really valid because doubt has been cast on the experimental evidence. It seems, therefore, that inhibition of the liver's power to produce ketones is a more likely hypothesis.

The final results of the experiments are as follows. The level of the blood ketone falls more rapidly in patients with diabetic ketosis when glucose and fructose are injected, in addition to insulin, than when saline and insulin alone are used. No significant difference could be discovered between the rates of fall of blood ketones when glucose or fructose was given. However, the degree of glycosuria was less with fructose, and the hyperglycæmia was less prolonged. Rosecan and Daughaday point out that one of the drawbacks of glucose used with insulin in the treatment of ketosis is that greater hyperglycæmia brings in its train greater intracellular dehydration; there is also diuresis due to greater osmosis, and more electrolytes are lost. They therefore consider that fructose properly used could minimize these disadvantages, and if used in conjunction with adequate dosage of insulin and fluid should hasten recovery.

Diabetes is a subject whose therapy has pursued a satisfactory and reasonably even course, though the type of insulin and choice of exact method still permit some latitude of opinion and practice. The handling of ketosis will, it seems, also cause further debate, and further work would be welcome to hasten its stabilization, as far as any subject can be stabilized in the practice of medicine.

[1] *J. Clin. Investigation*, January, 1954.

DROWNING HÆMOGLOBINURIA.

MORE efficient methods of resuscitataion of persons apparently drowned have afforded more opportunity for making observations on the physiological changes which may follow the admission of water to the circulation. It has been shown in both drowned individuals and in experimental animals that fresh water may gain access to the lungs and thus to the circulation. Charles E. Rath now presents a report on a fifteen-year-old boy in whom hæmoglobinæmia and hæmoglobinuria were observed during his recovery from submersion.[1] Rath's report is all the more interesting since he has not found any similar account in the literature dealing with a patient who survived submersion. The boy was found lying in a swimming pool, having been there for an unknown period, thought to be not more than five minutes. Voluntary respiration was resumed at once when artificial respiration was applied, and oxygen was given while he was being removed to hospital. Here he was restless, exhaling sanious froth, and scattered râles were audible in the lungs. Dark urine was passed; it contained protein, some red cells and many white cells, and tests showed the presence of blood pigment. Full investigation was made of the blood and urinary chemistry. Perhaps a warning may be found in his rather alarming reaction to the intravenous administration of "Sodium Amytal" for the purpose of facilitating lumbar puncture. He lost the customary evidences of reflex activity and showed signs of anoxia. These signs subsided, and during this period signs of the so-called decerebrate rigidity were manifest, but on the following day the boy had regained memory and ordered speech. After this he made a rapid recovery. The evidence of hæmolysis soon disappeared from the serum, and the urine also cleared. Rath, in studying this history, asks whether the mechanism of the hæmolysis was concerned with the passage of fresh water through the pulmonary alveolar walls or some other phenomenon. There was also the question of the cause of the signs of involvement of the central nervous system, and that of the possibility of renal damage. It seems unlikely that any serious lesion of the kidneys occurred, as the blood nitrogen level was raised only during a brief period, and the urinary signs observed could be due simply to a transient ischæmia. In an endeavour to explain the cause of the hæmolysis Rath had tests carried out on the red cell fragility, but no abnormality was found. The cold agglutination titre was not increased, and no history of hæmoglobinuria existed. Rath has also examined the literature, and performed three brief experiments in which water was allowed to enter the trachea of an experimental animal. These permitted a rough estimate of the amount of water which gained access to the blood. It was found that a rise in the plasma hæmochromogen level occurred even though the amount of water used was not sufficient to produce hæmoglobinuria. An experiment was also performed with water "labelled" with sodium salicylate. It seems difficult to establish a mathematical basis for the observed phenomena, but Rath is satisfied that the experi-

[1] *Blood*, December, 1953.

mental work of others points to the cause of hæmoglobinæmia in drowning being intravascular hæmolysis produced by the absorption of hypotonic fluid (that is, water) into the circulation. The sequel to this interesting case history is satisfactory, for the patient was followed up by the author, and remained well after periods of two weeks, one year, two years and, finally, four years from his admission to hospital. In conclusion, it may be mentioned that other recent investigators have compared the findings in animals drowned in fresh and in salt water. Electrolytic changes have been found in the blood in the left side of the heart, and it is suggested that this is due to failure of the heart to move pulmonary blood into the left auricle. Here, too, there seems good evidence of the passage of the drowning medium through the pulmonary alveolar walls. It is perhaps not out of place to emphasize the literally fatal ease with which young children may succumb to immersion, a hazard which is often preventible.

HUMAN MELANIN.

IT has long been known that melanin is produced from tyrosine by the action of an enzyme, tyrosinase producing dopa, dihydroxyphenylalanine, and the action of another enzyme or group of enzymes on the dopa to produce the black pigment, melanin. T. B. Fitzpatrick and A. B. Lerner[1] have done a considerable amount of work over the past few years on the production of melanin in human skin and on the various factors which influence its production. They suggest that the total enzyme systems concerned in the production of melanin from tyrosine be called tyrosinase. Melanin is a brown or black pigment produced by the polymerization of oxidation products of orthodihydroxyphenyl compounds to insoluble substances of high molecular weight. The tyrosinase system has been demonstrated in human melanomata, but only recently in normal human skin. It was shown by the authors that certain dendrite-shaped pigmented cells forming a syncytium along the epidermal-dermal junction were the only cells in the skin in which tyrosinase activity could be demonstrated, and the term melanocyte is proposed for these cells, the old term melanoblast being reserved for the immature cells at their origin in the neural crest. Melanocytes may occur in the dermis in compact cellular masses (blue nævi) or as groups of cells scattered through the dermal connective tissue (Mongolian spot). The melanocytes arise from the neural crest, and these cells in the dermis probably represent arrested migration from the neural crest. Melanocytes are also found in the human leptomeninges.

Copper is essential for the tyrosine-tyrosinase reaction, and the reaction in human pigment cells is inhibited by agents which combine with copper. A unique regulating mechanism for melanin production in mammalian melanocytes is provided by compounds containing –SH groups which probably bind the copper. Glutathione is such a substance. It has been suggested that the reaction between tyrosin and tyrosinase in normal human skin may be prevented or partly prevented by the presence of –SH groups. Physical agents (ultra-violet rays, X rays, radium and infra-red rays) and possibly inflammation may oxidize the –SH groups, thereby releasing the enzymes. Certain organic sulphur compounds have marked inhibitory effects. Thiouracil has been shown to decrease the concentration of melanin precursors in the urine of patients with malignant melanomata and to produce areas of depigmentation in the skin of Negroes. Certain parahydroxyphenyl compounds have a like effect, and the monobenzyl ether of hydroquinone and parahydroxypropiophenone have been used clinically with considerable success as depigmenting agents in man. The net content of melanin in the melanocytes of the skin determines whether the skin is black, brown or white, and depends on the balance of melanin formation and melanin excretion from the pigment cell. Part of the excretion goes via the lymphatics into the venous system and thence into the urine. In patients with Addision's disease and in Negroes melanin is often found in liver and kidneys. Another path of excretion is through the epidermis. A difference in the physiological turnover of melanin in white skin and Negro skin is apparent in the degree of depigmentation after local application of inhibitors of melanin formation. Local application of monobenzyl ether of hydroquinone often causes complete depigmentation in Negro skin, but not in normal white skin. This must be related to the greater excretion rate in Negroes. There is evidence that melanin production is controlled by the pituitary through the adrenals, for pigmentation can occur in patients receiving some preparations of corticotropin (ACTH).

Pigmentary disturbances are associated with blocks in the intermediary metabolism of phenylalanine and tyrosine. Decreased pigmentation in phenyluria occurs because of a relative deficiency of tyrosine. Lack of melanin in albinism is related to absence of the enzyme tyrosinase, although melanocytes are present in the skin. The pigmentation in alcaptonuric ochronosis is not due to melanin, but is derived from homogentisic acid.

[1] *Arch. Dermat. & Syph.*, February, 1954.

WOUND HEALING WITHOUT DRESSINGS.

ALTHOUGH individual surgeons have dispensed with the use of dressings for operation wounds in certain cases, this time-honoured practice is still generally observed. It has much to commend it. According to C. J. Heifetz, F. O. Richards and M. S. Lawrence,[1] the chief reasons for applying dressings are for absorbing secretions, aiding hæmostasis, splinting, obliterating dead spaces, protecting against trauma and preventing contamination. Without attempting to question the validity of using dressings or impugning the fundamental precepts just mentioned, Heifetz, Richards and Lawrence set out to determine whether the application of a dressing *per se* had any significant effect on wound healing. The investigation was both experimental and clinical. They produced clean aseptic wounds of the abdominal walls of rabbits, obtained hæmostasis and carefully coapted the edges; the wounds of half of the animals were left uncovered, and the others were covered with dressings. The wounds in the two groups healed equally well. Similarly, in a controlled study of 53 undrained aseptic surgical wounds in human subjects, no significant difference in healing of the wounds was noticed, and there was no significant difference in bacterial counts from the wounds. Three groups of patients were studied; in the first a dressing was applied and secured with adhesive tape, in the second group the dressings were removed after twenty-four hours, and in the third group no dressing was applied, but the wounds were covered with a sterile towel for six to twenty-four hours. It is pointed out that, apart from the question of healing of the wound, there are advantages in leaving off the dressings. These include the facts that the wound is more easily observed, that adhesive tape irritation is avoided, and that economies are possible in surgical supplies and in time of hospital personnel. Heifetz, Richards and Lawrence conclude, however, that a dressing should still be used if the operation has been performed under local anæsthesia, if a drain tube is inserted, if the wound is through the scar of a previous operation, if hæmostasis is not quite perfect, if the wound is closed with catgut, if there is any actual or potential dead space in the wound, if splinting is required, or if the wound may be subject to trauma because of its location or because of the uncooperativeness of the patient. The desirable treatment for an individual wound is a matter for selection.

[1] *Arch. Surg.*, November, 1953.

THE WORLD MEDICAL JOURNAL.

IN 1949 The World Medical Association commenced publication of a quarterly *Bulletin*, which was continued till October, 1943. At the last General Assembly of The World Medical Association in 1953, the *Bulletin* was the subject

of considerable discussion, and it was considered that its usefulness and influence could be extended. The matter was gone into further, and the outcome is that the *Bulletin* now no longer exists; it has been replaced by the *World Medical Journal*, which is the official journal of The World Medical Association. This journal is to be published bimonthly, with the hope that eventually it will appear each month. It has an executive editor (Dr. Austin Smith, the editor of *The Journal of the American Medical Association*), a business manager (Dr. Louis H. Bauer, the secretary-general of The World Medical Association) and an editorial advisory committee consisting of Dr. Paul Cibrie, of France, Dr. Hugh Clegg, of England, and Dr. Lorenzo Garcia-Tornel, of Spain, in addition to the executive editor and business manager.

The January, 1954, issue of the *World Medical Journal* is number one of volume one. It has a pleasing format, and its subject matter, which is presented in English, French and Spanish, is of considerable interest. In addition to information about The World Medical Association, its officers and its members, it contains original articles, book reviews, letters from Canada and from France, and general editorial matter. The original articles number three. John Pringle, Public Relations Officer of the British Medical Association, contributes a thoughtful discussion on relations between the medical and non-medical Press, Gunnar Gunderson, chairman of the executive committee of the Board of Trustees of the American Medical Association, writes on medical aspects of social security, and Leo H. Bartemeier, Associate Professor of Clinical Psychiatry in the University of Michigan, describes progress in psychiatry and the utilization of its principles in the daily practice of medicine.

It is hoped to develop the *World Medical Journal* according to the expressed wishes of its subscribers, and suggestions are welcomed. The World Medical Association, whose membership consists of national medical societies, is unique in that it represents non-governmental agencies. Its opportunities and its responsibilities are large and important, and it warrants and needs the support of all practising members of the medical profession. One way of knowing more about it and of supporting it is to subscribe to the *World Medical Journal*.

ANO-RECTAL COMPLICATIONS IN "MYCIN" THERAPY.

WITH the more extended use of aureomycin, "Terramycin" and "Chloromycetin", a variety of undesirable side effects of the therapy is appearing. S. D. Manheim and R. M. Alexander[1] have reported on 300 patients who have been treated with these drugs for a considerable variety of illnesses and who have developed ano-rectal complications as a direct result of the therapy. It is a commentary on the use and availability of these drugs in the United States that 208 of the 300 patients took one or other of these drugs for such common ailments as colds, sore throats, "virus infections" and "flu" often without medical advice. In all these cases the use of the drug was probably unjustified. Only five of the 300 patients were aged under twenty-one years, and, as these drugs are very widely used in the treatment of children, it would seem that children are not so susceptible as adults. Aureomycin was the most common offender, "Terramycin" next and "Chloromycetin" the least common.

The most common group of symptoms included perianal itching, burning, bleeding, a feeling of continuous moisture and fæcal staining of the underclothing. This syndrome usually arose one to two weeks after the ingestion of the drug, and in about 40% of cases followed a short period of diarrhœa. The symptoms were accentuated during the day, and rarely was there any discomfort at night. Perianal erythema extended for a distance of one to two inches around the anal fissure, and the skin exhibited multiple excoriations and superficial fissures. The appearance of the skin was very different from that seen in idiopathic *pruritus ani*. Some of the patients developed abscesses, fistulæ and anal ulcers. In the patients with pruritus and no complications, prompt relief was frequently obtained by the application of fungicidal powders and oral ingestion of buttermilk, yoghurt or acidophilus milk. Over two-thirds of the patients developed recurrences after apparent cure without further ingestion of the drug. This condition is evidently due to a monilial infection resulting from the overgrowth of Monilia in the intestine after the destruction of the normal intestinal flora by the "mycin" drugs. Such a condition in the alimentary tract has often been shown to occur during treatment with these drugs. Striking features of the syndrome described are its tendency to recur and its tenacity. In one case aureomycin lozenges were taken for one day for a mild sore throat, and yet this patient had recurrent symptoms for over twenty-four months. The authors stress the importance of using aureomycin, "Terramycin" and "Chloromycetin" only when specific indications exist, for the complications which develop as a result of oral ingestion are far more annoying, and in some cases more serious, than the original condition for which the drugs were given.

[1] *New York State J. Med.*, January, 1954.

TREATMENT OF POLYCYTHÆMIA WITH RADIOPHOSPHORUS.

THE treatment of *polycythæmia vera* with radioactive phosphorus is now established as the most effective method which has been employed up to the present time. This form of treatment has been in use since 1943, but no complete examinations of the blood have been reported. J. D. Abbatt, H. Chaplin, J. M. M. Darte and W. R. Pitney[1] have reported on 27 cases. They were particularly concerned to ascertain whether the platelet response was comparable to that which follows external X-irradiation, and whether there was any correlation with the clinical response. Careful measurements of plasma volume and red-cell mass were made in order to ascertain whether any constant pattern was present in patients with *polycythæmia vera*. The patients were given a single intravenous injection of five to eight millicuries of ^{32}P as inorganic phosphate without previous venesection. The full pattern of satisfactory response to a single injection of ^{32}P was not manifest for three or four months after treatment; but considerable symptomatic relief frequently occurred within a few days of the injection and before any objective evidence of response was obtained. As with external X-irradiation, the platelets have been shown to be the cellular element of the peripheral blood most sensitive to the administration of ^{32}P. A correlation between the degree of platelet depression and the incidence and completeness of ensuing remissions has been observed. This may serve as a useful guide to the need for additional treatment. Poor correlation was observed of elevation of hæmatocrit values with elevation of total blood volume. Some patients reported a considerable symptomatic improvement within two to four weeks of radiation therapy, before any change in hæmatocrit values had occurred. It is particularly important that patients who are liable to hæmorrhage be diagnosed and treated as early as possible, since if they are untreated they are liable to further hæmorrhage and its attendant dangers, whatever the hæmatocrit level may be. Moreover, it is probably the patient with hæmorrhagic and thrombotic tendencies who derives the most benefit from treatment, if benefit is measured in terms of prolongation of life. The authors found no advantage from limitation of dietary iron intake and venesection, but found that the single injection method gave clinical results at least equal to the best reported by other workers. It is recognized that the treatment is not curative.

[1] *Quart. J. Med.*, January, 1954.

Abstracts from Medical Literature.

MEDICINE.

Calf Circumference and Thrombophlebitis.

A. DAMON AND R. MCFARLAND (*J.A.M.A.*, October 17, 1953) have measured calf circumference in 369 healthy white men and in 109 consecutive subjects of acute thrombophlebitis. Normal men whose ages ranged from twenty to sixty-four years had an average calf-girth difference of 3·2 millimetres, right exceeding left. Similar measurements for 104 healthy white women showed no difference between the calves. The authors state that in the diagnosis of thrombophlebitis the most practical upper limit of normal calf difference appears to be ±15 millimetres in men and ±12 millimetres in women. Calf-girth difference in about 4% of normal men and 80% of thrombophlebitic men exceeds ±15 millimetres. In 1% to 2% of normal women and in 77% of thrombophlebitic women it exceeds ±12 millimetres. Variable individual ability to discern calf inequality and the difficulty of trained anthropologists in estimating 10 to 15 millimetre differences in calf size make routine measurement desirable in cases of suspected thromboembolic, neuro-muscular, and bone or joint disease.

Periodic Disease.

HOBART A. REIMANN (*Arch. Int. Med.*, October, 1953) presents further observations on periodic disease, a recurrent malady with protean manifestations first described in 1948. The essential feature is the occurrence at intervals, frequently rhythmic, of such symptoms as fever, abdominal pain, chest pain, arthralgia, cutaneous eruptions, renal colic, cyclic vomiting, sialorrhœa, œdema and neutropenia. The onset often dates from infancy, and the cause is unknown. Between attacks the patient is perfectly well. The disease may be familial and seems to occur more often in those of Jewish and Armenian extraction. In the Near East it is called "Armenian disease". Symptomatic relief is sometimes obtained from aspirin, ACTH or cortisone.

Œsophageal Varices.

H. D. BENNETT, C. LORENTZEN AND L. A. BAKER (*Arch. Int. Med.*, October, 1953) report on 12 closely studied patients with transient œsophageal varices due to hepatic cirrhosis. In five of the patients, four of them chronic alcoholics, the varices disappeared without any intervention other than medical therapy. These patients had hepatomegaly with little or no ascites. Liver function tests showed minor abnormalities only. Pathologically (liver biopsy) they were shown to have fatty liver or early Laennec's cirrhosis. Two patients had inflammatory disease of the œsophagus and surrounding tissues in addition to cirrhosis and œsophageal varices, and the varices subsequently disappeared. The remaining five patients with cirrhosis and varices were submitted to laparotomy, and on measurement, portal venous pressures were normal. Four of them had had gastro-intestinal hæmorrhage. Splenectomy was performed on four of the five patients, and in all of them the varices disappeared after operation. It is therefore concluded that neither portal hypertension nor œsophageal varices are necessarily permanent. The authors state that it has not proved possible to predict in which patients varices will regress, and it is therefore advised that in some circumstances repeated œsophagoscopy be carried out in order to detect changes in the size of œsophageal varices before performing surgery for portal hypertension.

Streptomycin and Tuberculous Children.

E. T. MCENERY (*J.A.M.A.*, October 17, 1953) reports on a five-year follow-up of 21 tuberculous children treated with streptomycin in the usual dosage for ninety to one hundred and twenty days. Eighteen of the children had a progressive primary pulmonary lesion. Three (all Negroes) had advanced adult type pulmonary tuberculosis. Of the 18 in the larger group, 15 are now perfectly well and can be considered cured. Two of those who died succumbed to tuberculous meningitis. In addition, two of the three children with the adult type of lesion died of progressive disease. It is concluded that progressive primary tuberculous lesions in children respond quickly and permanently to streptomycin. With the adult type of lesion the prognosis is not so good, and other measures must be used in addition to streptomycin.

Hepato-Lenticular Degeneration.

F. L. SULLIVAN, H. L. MARTIN AND F. MCDOWELL (*Arch. Neurol. & Psychiat.*, June, 1953) present the history of a family of seven children of whom five, including one pair of twins, have had progressive hepato-lenticular degeneration. The case histories of two of the patients, still living twenty-one years after the onset of symptoms and presenting both clinical and biochemical evidence of this disorder, are reported in detail. The twins exhibit a characteristic low serum copper concentration, but no such abnormality can be demonstrated in the unaffected members of the family.

X-Ray Findings in Tuberous Sclerosis.

H. I. BERLAND (*Arch. Neurol. & Psychiat.*, June, 1953) describes the radiological findings in tuberous sclerosis or epiloia. He presents reports of eight cases of the disease, illustrated by numerous skiagrams showing the bony changes. He states that the X-ray finding of calcification within the brain in this disease is well known, but less attention has been given in the literature to the bony changes which occur. The areas of calcification of the skull and brain found in tuberous sclerosis are multiple and bilateral. They vary in size and shape and may be within the bones of the calvaria or in the brain. The osseous changes in the hands and feet are of more significance than was formerly believed. The diagnosis of tuberous sclerosis should always be considered in the presence of (i) cyst-like lesions in the phalanges, (ii) irregular thickening of the cortex of the metatarsal bones, or (iii) irregular thickening of the cortex of any of the bones of the hands or feet associated with fragmentation or cyst-like changes. When these findings present themselves with calcification within the skull, the diagnosis of tuberous sclerosis can be clearly established. The percentage of the cases in which both these changes are present can be estimated to be between 60% and 65%. The author also describes other conditions producing calcification within the skull that must be distinguished from tuberous sclerosis. They include multiple telangiectasis, meningioma, calcified subdural hæmatoma, tuberculoma, hæmangioma of the skull, toxoplasmosis, Hippel-Lindau disease and neoplasms.

Neurological Illness following Vaccination.

H. G. MILLER (*Arch. Neurol. & Psychiat.*, June, 1953) reports 27 cases of neurological illness following Jennerian vaccination. In 16 of these cases the disease was purely encephalitic. There were five cases of encephalitis with associated signs of involvement of the spinal cord or nerve roots, three of transverse myelitis, and three of focal cerebral lesions without evidence of encephalitis. In eight cases of the encephalitic group death occurred within hours or days of the onset of the illness. Residual organic signs of the illness were frequent and included paraplegic, hemiplegic and radicular syndromes, dysarthria, epilepsy and involuntary movements; but in few cases was any serious physical disability found on reexamination after several years, and there were no instances of progressive nervous illness, except one of coincidental post-encephalitic Parkinsonism. Psychiatric sequelæ were more common and often disabling. The author discusses the nature of the focal cerebral illnesses and suggests that such illnesses may arise from thrombosis in arteries or veins which are the seat of inflammatory change. He considers the respective roles of physical or emotional factors in the causation of psychiatric sequelæ.

Vomiting of Pregnancy.

H. S. LANS *et alii* (*J.A.M.A.*, November 14, 1953) discuss hypokalæmia due to persistent vomiting during pregnancy. They state that 50% of pregnant women vomit. The cause should be sought. The loss of potassium due to vomiting may be important. The authors describe eight cases of this kind. Exhaustion and stupor were common. The blood potassium level was usually between 2·9 and 3·4 milliequivalents per litre, the normal value being from 4·0 to 5·6 milliequivalents per litre. Intravenous administration of potassium chloride and dextrose solution, usually with sodium chloride, was effective in restoring patients to normal. Three grammes of potassium chloride are added to each litre of fluid for parenteral use, so that the patient receives nine to fifteen grammes of potassium chloride a day until the serum potassium level has been normal for a day.

Isoniazid in Childhood Tuberculosis.

GLADYS BOYD, T. E. ROY AND A. JOSIUKAS (*Canad. M. A. J.*, September, 1953) discuss isoniazid in childhood tuberculosis. They review the history of the development of the isonicotinic acid derivatives, and analyse the results of its use in treatment in 50 patients

with childhood tuberculosis. The cases included the following types of infection: meningitis (10), tracheo-bronchial ulceration (10), miliary lesions (4), extensive pulmonary disease (5), massive mediastinal glands (6), pleural effusions (7), pericarditis (8) and surgical. The authors state that isoniazid is a drug with a profound effect on the human tubercle bacillus. Most of the organisms are sensitive to the drug, and do not lose this sensitivity for some months. Oral administration produces good plasma levels and, in the presence of meningitis, good spinal fluid levels. There seems no indication for parenteral treatment with the drug. It produces rapid initial beneficial effects in most cases, even if this is not maintained and other drugs have to be added later. Cortisone-like or adrenogenic effects are noted fairly often. In a few cases they are marked. The drug may cause increased ketosteroid excretion over a period of months. It should not be used without streptomycin in meningeal infections; in early cases of the disease, it may eliminate the necessity for intrathecal therapy. Streptomycin is given by the intramuscular route alone. Isoniazid should not be used in far advanced cases of meningitis because of its additional disturbing effect on the electrolyte balance and its tendency to produce convulsions. To date, its most striking regular effect has been on tracheo-bronchial ulceration.

Nor-Adrenaline in the Shock of Myocardial Infarction.

DANIEL G. CALENDA, JOSEPH F. URICCHIO AND LESTER M. FRIEDMAN (*Am. J. M. Sc.*, October, 1953) describe their experiences in giving intravenous infusions of *l*-nor-adrenaline in dextrose solution to patients in a state of shock following myocardial infarction. In four cases they thought that the effect was life-saving, but the overall mortality in their 13 cases was not reduced by treatment.

Treatment of Myxœdema.

R. W. RAWSON *et alii* (*Am. J. M. Sc.*, October, 1953) tested three drugs in one case of myxœdema. Diiodothyronine had no beneficial effect. Triiodothyronine had effects which were similar and equal to those of thyroxine, but the response was quicker and shorter.

Rheumatoid Arthritis.

E. R. MOVITT AND A. E. DAVIS (*Am. J. M. Sc.*, November, 1953) describe the results obtained from liver biopsy in cases of rheumatoid arthritis. They state that hepatic impairment has been reported by several authors. It has been suggested that liver dysfunction, if evident, may be the result of treatment with gold or other liver-toxic substance. The authors refer here to 17 cases of rheumatoid arthritis; all the patients were males between twenty-six and fifty-nine years of age. Liver tests showed an increase of serum globulin content in nine cases, and of γ globulin in 11. Other tests, such as the thymol turbidity test, serum bilirubin determination, cephalin cholesterol flocculation, bromsulphalein dye excretion, alkaline phosphatase determination and plasma prothrombin concentration, gave negative results. Liver biopsies on the 17 patients showed little departure from the normal. Slight and moderate fatty infiltration were recorded in three cases. The authors state that there was often no correlation between the results of liver function tests and anatomical findings. Liver function is apparently little affected in rheumatoid arthritis.

Cortisone in Shoulder-Hand Syndrome.

OTTO STEINBECKER, DAVID NEUSTADT AND LYON LAPIN (*J.A.M.A.*, October, 1953) believe that stellate ganglion block and cortisone or ACTH are the most helpful non-surgical methods of treating the shoulder-hand syndrome which sometimes follows myocardial infarction. They have had experience in 126 cases. They state that the results of treatment with stellate ganglion block were, if anything, a little better than those with cortisone; both forms of treatment were better than simple conservative treatment.

Pneumonia.

R. AUSTRIAN, R. ROSENBLUM *et alii* (*Am. J. M. Sc.*, November, 1953) describe the effects of erythromycin ("Ilotycin") in the treatment of pneumococcal pneumonia. Fifty patients were studied; 24 were treated with erythromycin and 26 with penicillin. Erythromycin was given orally in doses of 400 milligrammes every six hours until the rectal temperature was below 99·6° F. for seventy-two hours. Penicillin was given in doses of 300,000 units of the aqueous sodium salt intramuscularly every six hours for the same period. The results were very similar. Complications were also much the same, and the number of deaths was similar in each case. In general, erythromycin was less satisfactory than penicillin because of its insolubility and the fact that it acted against a limited number of bacteria. Its use was only justified when laboratory diagnosis was possible.

Electrical Activity of the Heart After Death.

A. PICK AND G. MININNI (*Brit. Heart J.*, October, 1953) report a case of sudden death from the intracardiac rupture of a dissecting aneurysm. Electrical activity of the heart persisted and was recorded for forty minutes after the patient's death.

Hypertension.

J. H. MOYER AND IRA JOHNSON (*Am. J. M. Sc.*, November, 1953) discuss "Veriloid" (given intramuscularly in aqueous solution) as a hypotensive agent. "Veriloid" is a mixture of the alkaloids of *Veratrum viride*, known also as "Alkavervir". It acts on the brain. It is useful in hypertensive crises occurring in bed patients. Thirty-five patients were treated; half of them had malignant hypertension. A dose of 0·6 milligramme was given intramuscularly, and if necessary the dose was increased by 0·2 milligramme until a hypotensive effect was obtained with a blood pressure about 150 millimetres of mercury, systolic, and 100 millimetres, diastolic. The effect lasted from three and a half hours to six hours. Hiccup, salivation, nausea or vomiting occurred in 50% of cases. Reduced doses were necessary when the optimum effect was produced. Oral treatment was not helpful. Intravenous treatment was effective but cumbersome.

Toxic Effects of PAS and Their Relief.

L. I. LEONARD (*Dis. Chest*, December, 1953) states that para-aminosalicylic acid with sodium bicarbonate is much better tolerated and gives rise to toxic symptoms of less severity than sodium para-aminosalicylate. He has found dimenhydramine ("Dramamine") of value in relieving toxic symptoms caused by PAS with sodium bicarbonate, but of little help in relieving those caused by sodium PAS.

Mitral Insufficiency.

C. P. BAILEY (*J. Thoracic Surg.*, December, 1953) describes an operation which he has performed on 70 or more patients to reduce mitral valvular incompetence. A strip of pericardium is threaded onto a special suturing probe, which is passed into the heart in such a way as to enable the defective valve to be sutured across the incompetent portion, which is usually posterior. The mortality from the operation was 25%, but it has been decreasing.

Tuberculosis After B.C.G. Vaccination.

G. DAHLSTRÖM (*Acta tuberc. scandinav.*, Supplement XXXII, 1953) has compared the incidence and course of tuberculous disease as it occurred among 61,474 conscripts to the Swedish army, 36,235 of whom were vaccinated with B.C.G. Of the vaccinated subjects 167 and of the unvaccinated subjects 321 developed one or more forms of tuberculosis. The course of primary tuberculosis appeared to be influenced favourably for the patient by the vaccination in those who nevertheless acquired the disease. Of the vaccinated subjects 62 and of the unvaccinated subjects 99 developed post-primary pulmonary tuberculosis. Among these there appeared to be no significant difference in prognosis.

Vagotomy.

W. WALTERS AND D. P. CHANCE (*J.A.M.A.*, November 14, 1954) discuss vagotomy as a prophylactic and curative procedure in peptic ulcer. They state that vagotomy for gastric ulcer has proved unsatisfactory in every respect. For duodenal ulcer gastro-enterostomy has given splendid results; but ulcers have recurred in 6% to 10% of cases or more. Gastric resection has taken the place of gastro-enterostomy, because only 2% of recurrences was experienced. However, gastric symptoms still recurred. The authors now advise vagotomy, which gave 76% of good results. Temporary healing of ulcers was observed. In 62% of cases the result was good. Vagotomy with gastro-enterostomy was the next form of treatment advised. Results were unsatisfactory in many cases. Nausea, fullness, diarrhœa and other symptoms were experienced. Vagotomy with pyloroplasty was unsatisfactory and was abandoned. Now a combination of vagotomy, gastric resection and re-resection is under way. It is said that vagotomy helps in the treatment of recurring ulcers, especially after gastric resection. The authors favour extensive surgical interference, including vagotomy.

Special Article.

THE ENTRY OF WOMEN INTO MEDICINE.

"A WOMAN may be registered as a medical practitioner (1876, 39 and 40 Vict. c. 41)." In 1954 there appears nothing remarkable about this sentence, taken from the "Encyclopædia Britannica" (Fourteenth Edition) in its section on the legal position of women; yet in actual fact it marks the beginning of the end of a struggle which started in 1845 in the United States of America, and which was intimately tied up with the educational and legal status of women. At this distance of time, when the tumult and shouting may be said to have died, it is possible to consider the events dispassionately, and to admire the courage, tenacity of purpose and, be it noted, the unspoiled femininity of the protagonists. The story has been told with impartiality and good humour by E. Moberly Bell,[1] who has made the central characters come alive against the background of the social and economic circumstances of the times in which they lived. The three who bore the heat and burden of the day were Elizabeth Blackwell, Elizabeth Garrett and Sophia Jex-Blake. The period was the early years of the reign of Queen Victoria; Great Britain was in the grip of an economic depression, which followed the Napoleonic Wars. The Industrial Revolution had brought about the complete disappearance of the family business, and this had had a profound effect upon the status of women. In the family business the wife took her share and much responsibility, and nobody thought it strange. Now it was considered genteel for a man's wife and daughters to live in idleness and to be very poorly educated. The young women who were able to go and work in factories fared best; they could earn quite large sums of money. The depression hit hardest at the "distressed gentlewomen", who were obliged to take positions as governesses, for which they were not well qualified, and in which they were poorly paid and rather despised. A serious view of the situation was taken by various religious organizations and by a number of enlightened men and women. They provided the impetus which brought about the social legislation of the nineteenth century; this need not be discussed further. The "distressed gentlewomen" provided two problems—to improve their educational quality and to provide other avenues of employment for them. *The Englishwoman's Journal* was founded in 1858 because the existing Press was hostile to any attempt at reform, and would not give the right sort of publicity. It was "a publication for women entirely managed and written by women". Most of the Press approved of it; it was described as "practical *though* feminine". The offices of the journal were inundated by women eager to help and by others clamouring for work. The enthusiastic young women who had started the ball rolling took rooms in Langham Place, where an employment register was begun. The difficulty in finding suitable work for the applicants led directly to the founding of businesses run by women for women. The stage was now set for further advancement. In the issue of the *Edinburgh Review* of April, 1859, appeared an article on female industry, in which the following statement was made:

> . . . From our youth up some of us have known how certain of the wisest and most appreciated of physicians have insisted that the health of women and their children will never be guarded as it ought to be till it is put under the charge of physicians of their own sex.

In 1859 the Medical Register was instituted, "not for the confusion of women, but for the protection of the public against quacks and quackery"; there was one woman's name on it—that of Elizabeth Blackwell, M.D. (Geneva, U.S.A.). She was able to be registered because of the clause in the *Medical Act*, 1858, which allowed anyone holding a foreign degree and practising in England in that year to claim registration. The next woman doctor's name was placed on the register in 1866, and it was another twelve years before a third was added.

Elizabeth Blackwell had been born in England, but had grown up in the United States. Her father believed in the equality of the sexes, and had all his children educated on the same lines. He died at the age of forty-eight years, leaving nine children, of whom Elizabeth was the third; she was then aged seventeen years. He also left considerable debts. Elizabeth took the lead, a school was opened, and after five years the family was in moderate comfort. In 1844 she determined on a medical career. Her decision was a curious one. She was a person of great vitality, impatient of sickness; but a friend who was dying of cancer said to her: "If I could have been treated by a lady doctor, I should have been spared half my suffering." Elizabeth at first recoiled from the idea that she should become a doctor; but as time went on it assumed the aspect of a great moral struggle, as her tentative inquiries about what to do to embark on such a career were met with disapproval and prejudice even from people whom she had expected to help her. However, there were those who were favourable to her project and willing to help. By 1847 she had earned enough money by teaching to maintain her through a medical course. One after another the heads of medical schools in Philadelphia to whom she wrote declined to receive her as a student. She then wrote to the heads of twelve medical schools in the northern States; the University of Geneva, a small town in New York, replied favourably. Its Medical Faculty, unwilling to take the responsibility of making a decision on such a revolutionary question, had passed her request on to the students, who passed a resolution that her application met with their entire approbation, and they pledged themselves that no conduct of theirs should cause her to regret her attendance at that institution. During her course she was conscious of a certain hostility from the wives of doctors and other people in the town; but she was so engrossed in her work that she paid no attention to it. She took her degree in January, 1849, having passed every course with honours. At the last moment the Senate of the University hesitated at the daring step it was taking by conferring on a woman a doctorate in medicine. The situation was saved by the Dean of the Faculty, who held a metaphorical gun at the heads of the members of the Senate. Elizabeth Blackwell on her graduation became news; even "Mr. Punch" saluted her with some verses. She later went to London, where she was well and courteously received, and even lionized; but in Paris things were different. The best she could do there in the way of gaining experience was to spend an uncomfortable period in a training school for midwives on the same conditions as the other students. There calamity overwhelmed her, for while she was syringing a baby's eye for purulent ophthalmia she infected one of her own, and the eye was lost. However, she accepted her misfortune with great gallantry, and went back to New York. We cannot in this place give a detailed account of her struggles for recognition in that city. The important thing is that, finding every avenue of gaining experience in a dispensary closed to her, she founded one of her own, and this was the forerunner of the New York Infirmary for Women and Children, which was formally opened in 1857. In 1858 she went back to England to deliver three lectures on "Medicine as a Profession for Ladies" under the auspices of the Langham Place group. Her friends in England wished her to stay there, but she felt that her work lay in America. However, she left the field prepared and a torch lighted in the hand of a "bright intelligent young lady" who had listened to her lectures—Elizabeth Garrett.

Elizabeth Garrett was the child of an enlightened father and a capable mother and was given a good education. She was twenty-three years old when Elizabeth Blackwell visited England, and had long been conscious of a desire for some satisfying occupation. Dr. Blackwell simply showed her that it was essential that someone should take the initial steps to open the door of medical practice to women in England, and from then Elizabeth Garrett realized that in spite of all the difficulties which would undoubtedly have to be faced, she was the one who must do it. Her father's somewhat scandalized attitude was soon changed to one of support when he saw the rather crushing way in which his daughter was received by the Harley Street consultants whom she approached, although he was never altogether happy about her plan. Elizabeth Garrett then applied to Dr. Hawes, of the Middlesex Hospital, who proved very friendly, and in 1861 she went to work at that hospital, ostensibly as a nurse; she was given all the facilities of a student, but the treasurer declined her fees, so that she could not be enrolled as a regular student for the whole course. She was, however, accepted for some special courses of lectures and demonstrations, and in the examinations at the end of the course gained a certificate of honour in each subject. Somehow the word went round, and hostility was aroused. The students sent a memorandum to the committee asking for her exclusion, and she was told that while she might finish the course of lectures for which she had paid, she must leave the hospital. In August, 1861, the Hall of Apothecaries intimated that it would examine women who had fulfilled the requisite conditions (apprenticeship

[1] "Storming the Citadel: The Rise of the Woman Doctor", by E. Moberly Bell; 1953. London: Constable and Company, Limited. Sydney: Walter Standish and Sons. 8½" × 6", pp. 200, with seven illustrations. Price: 18s.

to a qualified doctor for five years and instruction from recognized university tutors in the syllabus). This surprising action on the part of the Hall of Apothecaries was not due to "sweet reasonableness"; it had taken counsel's opinion on the wording of a portion of its charter, which had been laid down in 1823. In that charter it was stated that the Hall of Apothecaries would examine "all persons" who conformed to the regulations. Counsel's opinion was that "persons" must be taken to include women. Elizabeth Garrett determined to work for the licenciate of the Society of Apothecaries, which would be enough to put her name on the Medical Register; but she knew she would not be satisfied with anything less than a doctorate in medicine, so that she might be as fully qualified as any man. Then began an assault upon the universities, the first being the University of London. No success was achieved there. At this point it should be noted that public opinion was becoming more and more in favour of the women, not only in their determination to study medicine, but in their attempts to gain admission to other university courses. Many of their staunchest supporters were men in high places, while many of their opponents were members of their own sex. Elizabeth Garrett was admirably adapted to being in the vanguard of the attack. She was patient and persistent, and indeed it might well have been of her that Samuel Butler the Younger wrote in his "Note-Books": "You can do very little with faith, but you can do nothing without it." The Universities of Oxford and Cambridge refused to admit women students, and Elizabeth Garrett then turned her attention to the University of St. Andrews. There she was able to attend some lectures, but finally the Senatus of the University decided to exercise its discretionary power to exclude whom it would, male or female, and excluded Elizabeth Garrett. There was no hope of being examined there. Next she tried Edinburgh, where she was permitted to work for a while under friendly lecturers; but the University was adamant and refused to admit her as a student. In all this time, from May, 1861, to July, 1863, she had had some valuable medical teaching, but she was no nearer her degree. Wisely she decided to make certain of her L.S.A., and secured from the Court of Examiners a resolution "that the Certificates on the various subjects required by the Court be obtained from recognized lecturers of acknowledged schools of medicine". That made her position clear, because she felt sure that she could obtain private teaching. For a time she was allowed to work at the London Hospital, but was very unhappy because of the constant hostility. She had some difficulty in securing her private coaching, because some of those whom she approached rejected her "indelicate" suggestion. By the autumn of 1865 she had passed all preliminary examinations with credit, and had completed the curriculum laid down. Therefore she applied to the Society of Apothecaries for examination. The Society tried to refuse, but her father threatened legal action, and so her opponents had to give way. Elizabeth Garrett passed the examination with credit, and thus became L.S.A. A year later her name was placed on the Medical Register. It is interesting to note that the Society of Apothecaries took steps to prevent the recurrence of such a disaster, and passed a resolution that candidates for their diploma must have worked in a recognized medical school.

Elizabeth Garrett had won her battle, and was now a qualified medical practitioner; but since the way by which she had entered the profession had been closed, the leadership in the campaign fell into other hands. It is here that the turbulent and dynamic Sophia Jex-Blake takes the centre of the stage. She was the youngest child of stiffly religious parents, and very much younger than her brother and sister, so that she suffered from all the disadvantages of an only child. In her young life she was completely thwarted and frustrated, because she could never fit into the Victorian pattern designed for her. At home and at school she was kept very conscious of her sins, but allowed no outlet for her keen intelligence and great energy, so that her health gave cause for concern (at one stage the diagnosis of "mental excitability" was made). She early showed an aptitude for mathematics. When she was eighteen years old she heard about Queen's College, and determined to go there. After a great many battles she got her own way, and, having once left home, she claimed her adult status and her right to conduct her own life on her own lines. She taught mathematics for a while at Queen's College, and then conceived the idea of reforming education. With this end in view she took a post in Germany, and then visited America. There she came under the influence of Dr. Lucy Sewall, one of Dr. Blackwell's disciples. They became friends, and Dr. Sewall, visiting England when Sophia returned home, charmed the Jex-Blake parents. Sophia went back to America, happy in the approval of her parents of what she intended to do. But shortly afterwards her father died; impetuously she returned home to be with her mother, abandoning all thought of doing a medical course. The mutual cherishing of mother and daughter soon became too much for both of them, and by January, 1869, Sophia had made up her mind to try to get a medical degree at one of the British universities. After much consideration and consultation, she decided upon the University of Edinburgh, where Professor David Masson, Professor of Rhetorick and English Literature, and Sir James Simpson were interested and sympathetic. Sophia went to Edinburgh, interviewed the Dean of the Faculty of Medicine, and then canvassed all the members of the faculty. A few promised her support, the majority were dubious; but the faculty recommended, and the Senatus approved, Sophia's admission to the classes for which she had applied, as an experiment. The admission was hedged around with provisos. She was allowed to prepare for matriculation. From now on the story of the fight becomes the story of the unseemly behaviour of the University of Edinburgh, the arch-villain appearing to be Professor Christison. (This story has already been told in the form of a novel, which was noticed in these columns on January 5, 1952.[1]) Four other women joined Sophia, and the five presented themselves for the matriculation examination and all passed at a standard considerably higher than that of the average man. In accordance with the decision of a meeting of the faculty held on July 1, 1869, the five matriculated in the ordinary manner and received the ordinary matriculation certificate. They had to pay about double the ordinary fees on account of the fact that they attended separate classes. Sophia spent six happy months, but it was too good to last. The idea of the inferior quality of the female brain was rudely shattered when the class lists were put up at the end of the winter session. No woman had failed, four out of five had gained honours, and one, Edith Pechey, had come top of her year in the chemistry examination, and was entitled to the Hope Scholarship. Professor Hope was in a quandary, because he had lectured to the women, letting them in and out of the lecture room by a side door lest anyone might suspect their presence; but he did not wish to wound the susceptibilities of the leading members of his faculty by awarding the scholarship to a woman. He therefore awarded to Edith Pechey one of the five bronze medals annually presented by the University to the five best students, and declared the man immediately below her on the list to be the winner of the scholarship, on the grounds that the women, having been taught separately, could not rank as members of the class. The logical deduction from this decision was that he could give none of them the certificates of attendance expressly stipulated for them in the University regulations, and necessary if they were to present themselves for the professional examination. The question of the scholarship was abandoned; but an appeal was made to the Senatus about the certificates. Somewhat illogically that body decided by a majority of one vote (*a*) that the women were entitled to the ordinary certificate of attendance at the chemistry class, and (*b*) that Edith Pechey was not entitled to the Hope Scholarship, as she had not been a member of the class. Edith Pechey was popular in Edinburgh, and the injustice of the decision caused the University to suffer severely in reputation. A serious attack was now made on the position of the women. It was led by Professor Christison, who was determined that they must be driven from the University. It might be said that no holds were barred, for the women were subjected to every possible indignity, including being pelted with dirt and decaying vegetation as they tried to go to lectures. The question of classes was solved by the Edinburgh Extramural School. This had existed since 1840, and consisted of medical classes conducted by fully qualified lecturers other than University professors. It was not bound by any resolution of the Senatus. In 1870 three of the lecturers admitted women to their lectures. The question of clinical instruction would have been solved by the reasonably liberal Committee of Managers of the Royal Infirmary; but Professor Christison was a manager, so that avenue was closed. Public interest was now thoroughly aroused, and the Committee for Securing Complete Medical Education to Women in Edinburgh brought all the pressure it could command to bear on the University to give the women all the necessary teaching. It would be impossible here to describe all the undignified expedients indulged in by the University authorities to avoid having to do this. It was time to invoke the law to see that justice was done. An Action of Declarator was brought and pleaded before the Lord Ordinary, Lord Clifford. In July, 1872, he gave a judgement in which he declared entirely for the women, and at last

[1] "Seven Against Edinburgh", by Muriel Masefield.

victory seemed within their grasp. The women were prematurely jubilant. They were busy working for their final examinations, and were not greatly troubled by the fact that the Senatus had appealed against the judgement of the Lord Ordinary. In June, 1873, in a judgement given by the Inner Court, the women's cause was defeated by a majority of seven to five. "The majority declared that the action of the Senatus in admitting women in 1869 was *ultra vires*, and that therefore the University had no responsibility whatever to the women whom they had accepted as matriculated students, and from whom they had taken fees greatly in excess of those paid by male students. According to this judgement the whole situation had arisen out of the illegal action of the Senatus in 1869. It is difficult therefore to conceive on what grounds the Court found it possible to lay the costs for both actions on the women. This, however, was done." This was the end of the fight in Edinburgh; but as Sophia Jex-Blake surveyed the ruins, she saw that much had been gained. The women had many staunch friends who had proved themselves; time and again the adverse majority had been very small; and not even a majority of the professors were in favour of the action of the University. Furthermore, the mental power of the female brain had now been proved not to be inferior to that of the (allegedly) larger male brain. Sophia Jex-Blake turned her attention to London. There Elizabeth Garrett was well established. In 1868 the University of Paris had opened its medical degrees to women, and in 1870 she had been successful in taking the Paris degree. In 1871 she married J. G. Anderson. It is difficult to imagine two temperaments so totally dissimilar as those of Elizabeth Garrett Anderson and Sophia Jex-Blake. Elizabeth Garrett Anderson hoped that the women would accept for the time the judgement of the University Court in Edinburgh, and said so in a letter to *The Times*. This infuriated Sophia Jex-Blake, who had had to do the hardest fighting, and she also wrote to *The Times*, an explosive letter. This was in 1873. In London she found many supporters, and out of it all grew the conviction that the only solution to the problem was the founding of a medical school for women. It is easy to imagine the difficulties with which those interested were confronted; indeed, they must have seemed insuperable. However, at a preliminary meeting of the Provisional Committee on August 22, 1874, a resolution was passed "that in the opinion of the present meeting it is desirable that a school be founded in London with a view of educating women in medicine and enabling them to pass such examinations as would place their names on the Medical Register". The Provisional Committee consisted entirely of registered medical practitioners; this was a self-denying ordinance on the part of Sophia Jex-Blake, since she had taken care to see that Elizabeth Garrett Anderson was on the committee. Thanks to the devoted energy of Sophia Jex-Blake, the school was opened on October 12, 1874, in a house in which George IV had kept one of his mistresses. There were 14 students, of whom 12 had been in Edinburgh. Three great problems faced the school: finance, the finding of an examining body to accept women, and the finding of some means of securing clinical instruction. In May, 1875, the Provisional Committee handed over to a permanent council, which consisted of all the members of the Provisional Committee, together with some men and women, not medical practitioners, who were of standing in the world of affairs and convinced supporters of the movement. All the 19 London examining bodies refused to place the school on their list of recognized medical schools. It had many friends in Parliament, and the battle was renewed. In 1875 Cowper-Temple reintroduced his Enabling Bill, which had been defeated in the previous session; this Bill was "to remove doubts as to the powers of the Universities of Scotland to admit women as students and to grant degrees to women". The Bill was again defeated, and it became obvious that the question cut across all ordinary party loyalties. In June an undertaking was given that the Government would consider the matter during the recess, with a view to legislation in the following session. The Lord President of the Privy Council sent a letter to the General Medical Council, asking for its observations on the general question of the admission of women to the medical profession. The debate that followed in the General Medical Council lasted for three days, and all the old arguments for and against were advanced. The comment of one surgeon summed it all up neatly: "It appears that it is most becoming and proper for a woman to discharge all those duties which are incidental to our profession for 30s. a week, but if she is to have three or four guineas a day for discharging the same duties, then they are immoral and immodest and unsuited to the soft nature that should characterize a lady." Finally a compromise resolution was carried, which concluded with the words: ". . . the Council are not prepared to say that women ought to be excluded from the profession." On the strength of this the friends of the women returned to the attack, and various further moves were made in Parliament. The last of these was an Enabling Bill introduced by Russell Gurney, the Recorder of London, which was submitted to the General Medical Council. The Council approved it on condition that it should be clearly permissive, and that no medical degree conferred by any university should give any right to any woman to sit on any examining body. The Bill passed all its stages and received the Royal assent on August 12, 1876. The question was now, which universities would act on the permission granted by Parliament to examine women for medical degrees. The students who had been at Edinburgh naturally turned to that University, which found a neat means of refusing by stating that the students in question had taken some courses of lectures at the Extra-mural School. The Irish College of Physicians and the Queen's University of Ireland agreed to admit women to examination and diplomas; moreover, the Irish College of Physicians was ready to consider the recognition of the London School of Medicine for Women. This recognition followed in February, 1877. This success was almost entirely due to the tact and charm of Edith Pechey, who went to Dublin as one of the emissaries. In 1877 Sophia Jex-Blake and Edith Pechey, who had already taken the M.D. of Berne University, presented themselves for examination in Dublin and were successful. Their names, together with those of three other of the Edinburgh women, were added to the Medical Register. But for the other students at the London School of Medicine for Women the problem of clinical instruction still remained. The Royal Free Hospital was close to the school, and had no clinical school of its own. The medical staff, on being approached, declined "to entertain the question"; but an approach to the lay members of the governing body was more successful. The hospital drove a hard bargain. The school had to pay over to the hospital all clinical fees received from the students, and to guarantee that the sum should not fall below £400 in any one year. It also undertook to pay a subsidy of 300 guineas per year in case the admission of women students should cause a falling-off in the income from subscribers. There was also a kind of five years' probationary period. Gradually suspicion was allayed, the tension eased and things worked smoothly. In 1878, after a great deal of discussion and opposition, a meeting of Convocation of the University of London accepted a new charter admitting women to all degrees of the university in complete equality with men. A delicate problem now arose, that of the working out of final relations with the Royal Free Hospital. Sophia Jex-Blake, who was at the time in Dublin taking her M.D. degree, had achieved miracles for the London School of Medicine for Women; but she was an autocrat, and even those who admired her most realized that she had no tact and could be dangerous. The Council of the School was about to make an appeal to the public for funds, reorganization was necessary and there had to be an officially appointed organizing secretary. Sophia Jex-Blake wanted the office. Both she and Elizabeth Garrett Anderson were proposed for the post, but a compromise was found in the appointment of Mrs. Isabel Thorne, who had been one of the original Edinburgh students, but had been prevented by family responsibilities from going to Berne to take her M.D. there. She was a friend of Sophia Jex-Blake. The latter took her defeat in a fine spirit, and went back to Edinburgh to start a practice there. In her youth she had recorded in her diary the prayer: "Put me utterly aside if need be." Now she accepted the answer to her prayer. The debt that all medical women owe to her cannot be over-estimated. In 1883 Elizabeth Garrett Anderson was appointed Dean of the school, much to the disappointment of Sophia Jex-Blake, who had hoped for the appointment, and from then on she gradually lost interest in the school. The school continued to grow, and to suffer all the discomforts and difficulties that go with growth; but it surmounted them all. A satisfactory arrangement was finally entered into with the Royal Free Hospital, and the school became the London (Royal Free Hospital) School of Medicine for Women. In 1944 the Goodenough Report was issued, and wrote "*finis*" to the struggle, although much tidying-up still remained to be done. By the implementation of the report, in 1947 the London (Royal Free Hospital) School of Medicine for Women became the Royal Free Hospital School of Medicine, to admit men and women on equal terms, as all other medical schools were now bound to do.

This, very briefly, is the story of the three who bore the brunt of the attack on the citadel in the English-speaking world—Elizabeth Blackwell, Elizabeth Garrett Anderson and Sophia Jex-Blake. Of their many able and devoted lieutenants, and of the enlightened men and women who

had faith in the cause for which they stood, little has been said in this summary; but Miss Moberly Bell's account is stirring and vivid. Much still remained to be done, and the story as it relates to the work in India, and to what happened during the Great War, well repays reading. In the latter connexion some mention should be made of the way in which the Suffragist Movement, to which many prominent medical women belonged, turned its attention from agitating for the franchise to the immediate business of serving the country. One important result was the organizing of the Scottish Women's Hospital, units of which saw service in several countries and endured great hardships. It may be recalled that Dr. Laura Hope, who qualified in Adelaide, and whose obituary notice was published in these columns on January 17, 1953, served with a unit of this hospital in Serbia, and was taken prisoner with the Serbian army. There also remained the opposition of the British Medical Association to the admission of women as members (there is considerable entertainment in this part of the story), the difficulties confronting medical women in obtaining post-graduate experience, and the obstacles that had to be overcome before they could successfully establish themselves in private practice. But the tide had really turned years before, and although the opposition was real and the difficulties were heart-breaking, they were not insuperable. The Goodenough Report did away with all discrimination between men and women in medical training, and "at the moment of victory the keys of the citadel were handed over with generosity".

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held at the Royal Children's Hospital, Melbourne, on December 9, 1953. The meeting took the form of a symposium on congenital heart disease, and was preceded by a clinical demonstration of congenital heart disorders in infants.

Embryological Approach to Congenital Heart Disease.

DR. ALAN WILLIAMS described in detail the embryology of the heart and the origin of congenital deformities resulting from interference with embryological development. The description was illustrated by means of photographic projections.

Patent Ductus Arteriosus: Surgical Results at Royal Children's Hospital.

DR. PETER JONES reviewed the results of surgery at the Royal Children's Hospital on children suffering from patent *ductus arteriosus* during the period 1947-1953 inclusive. Over the seven-year period 70 children had been treated surgically for patent *ductus arteriosus*; 55 were girls and 15 were boys. Of those children 53 were symptomless. In 25 cases the abnormality was detected on routine examination, whilst in 28 it was detected on examination for a coincident condition. Only 17 children presented with symptoms referable to a patent *ductus arteriosus*. The annual number of children treated by surgery had increased steadily over the seven-year period, and had reached 31 in 1953.

Of the 70 children one was less than one year of age (being aged six months) and successfully survived the operation. Two children were in the age group of one to two years. One, aged thirteen months, died from cardiac arrest during induction of anæsthesia; this child had a history of syncopal attacks, and electrocardiography had revealed a Wolff-Parksinson-White syndrome. The other child in the same age group obtained a successful result. There were 12 children between the ages of two and five years; none of them died. In the age group of five to ten years 32 children were subjected to surgery with one death; whilst in the age group of ten to fifteen years 23 children had operations, and one failed to survive.

DR. RUSSELL HOWARD, in referring to the 17 children in whom symptoms were referable to patent *ductus arteriosus*, stressed the fact that the symptoms were not recognized on first presentation as being typical of patent *ductus arteriosus*. It was considered that they were due to that condition in retrospect only when, after surgery, they were no longer present. Even atypical symptoms such as anorexia were thus shown to have disappeared.

Dr. Howard then briefly commented on the "disasters" in the group of patients. He said that in operating on the second child of the series he had ligated the left pulmonary artery instead of the *ductus arteriosus*. Post-operatively it was thought that the persistence of a thrill was due to an aortico-pulmonary septal defect. However, it was demonstrated by angiocardiography that the pulmonary artery had been ligated. The *ductus arteriosus* was tied successfully on a subsequent occasion. One child had bled during the operation, and it had been necessary to stop the hæmorrhage with clamps, which were left *in situ*. On subsequent removal of the clamps the hæmorrhage had recurred and the child had died. One child had died from cardiac arrest after the ductus had been tied, and an infant of thirteen months, whose case Dr. Jones had mentioned, died during induction of anæsthesia with cyclopropane. That child had a history of syncopal attacks associated with a Wolff-Parkinson-White syndrome. Recanalization of the *ductus arteriosus* had developed in one child, who had been operated upon eight months previously. The ductus of that child was broad and short. It was ligated in three places, but after eight months there was definite evidence of recurrence. Dr. Howard said that the current practice was ligation of the ductus, not division, but in certain cases of patent *ductus arteriosus* division was required. The procedure was often very difficult and sometimes risky. Gross divided the ductus in all cases.

DR. M. L. POWELL said that it was considered that children with patent *ductus arteriosus* were symptomless because parents did not realize that symptoms existed. Sometimes it was difficult to persuade parents that surgery was necessary. In three cases, chronic cough was the presenting symptom. That disappeared on each occasion after ligation of the *ductus arteriosus*. Spontaneous closure of a patent *ductus arteriosus* had not been recorded. There was no indication to temporize with surgery. In reference to the diagnosis of patent *ductus arteriosus*, Dr. Powell said that careful listening in absolute silence for the typical machinery murmur stood out as the most important diagnostic procedure. Referring to the infant with the Wolff-Parkinson-White syndrome who had died from cardiac arrest, Dr. Powell said that he thought that the child should have received pre-operative digitalization.

Aortic Vascular Ring.

DR. RUSSELL HOWARD presented a male child, aged three years, in whom an aortic vascular ring had been divided. Four times in the preceding twelve months the child had had a severe upper respiratory tract infection with tracheitis. On each occasion, severe stridor had developed, and once some cyanosis. The stridor had occurred both on inspiration and on expiration. In between attacks respiration had been normal, except after violent exercise or crying, when slight stridor had been noticed.

Examination of the child showed that he was apparently normally developed and robust and without apparent cardiac anomaly. A skiagram of the chest showed that the arch of the aorta was on the right side, and radiological examination after the ingestion of barium showed a marked indentation of the œsophagus posteriorly and on the right side at the level of the arch. Angiocardiography demonstrated that the ascending part of the aorta was on the right side, passing posteriorly behind the œsophagus to reach the left side at the commencement of the descending part of the arch. At that point a bulge was present, from which arose the left subclavian artery. The left common carotid artery arose just proximal to that. It was considered that the child had an aortic vascular ring, and from the angiogram it was thought that the ring was completed on the left side by the *ligamentum arteriosum* passing forwards from the aortic bulge to the pulmonary artery.

Dr. Howard said that he considered that the lesion was a progressive one, requiring surgery. At operation, it was found that the anatomy was just as had been anticipated from the investigations. The usual left postero-lateral incision was made, and the thorax entered through the bed of the resected fourth rib. The *ligamentum arteriosum* was situated in the position which investigations had suggested, and was divided between ligatures, fairly readily. The divided ends immediately sprang apart, indicating that there had been tension in the vascular ring. The improvement was immediate, and was noticed by the anæsthetist, who commented that the stridor, which had been present when the child cried immediately prior to induction, was absent when he cried whilst coming out of the anæsthetic. Since operation the child had had one severe upper respiratory tract infection, with tracheitis, and neither distress nor stridor had occurred.

In conclusion, Dr. Howard said that the abnormality from which the child had suffered was an example of one of the

two more common forms of vascular obstruction of the trachea and œsophagus, the more common type being a double aortic arch. However, all types of that condition were amongst the rare congenital vascular anomalies.

Failure to Thrive in Early Infancy due to Patent Ductus Arteriosus.

DR. M. L. POWELL described the case reports of three infants who had presented with the features of failure to thrive and upper respiratory tract infection. All three infants suffered from patent *ductus arteriosus*.

The first infant, aged three months, had been full time at birth, and the mother had had no illnesses during her pregnancy. Since birth the infant had increased only 12 ounces in weight, so that at the age of three months she weighed seven pounds nine ounces. She had a slight cough and rapid respiration, but no cyanosis. On examination of the child, a continuous rough cardiac bruit with a loud split second sound was heard. It was most easily audible over the "surgical" area, namely, the second left intercostal space. A skiagram of the chest showed some cardiac enlargement, but not a particularly full pulmonary segment. The systolic blood pressure was 130 millimetres of mercury, whilst the diastolic pressure was unrecordable. Both femoral and radial pulses were very easily palpable. An electrocardiogram showed no axis deviation. Dr. Powell said that he considered that the infant had a patent *ductus arteriosus*, producing failure to thrive and possibly aggravating a respiratory tract infection.

The second infant to be presented was aged four weeks. The mother had had rubella when three weeks pregnant. The baby had gained only seven ounces since birth, and when examined weighed six pounds nine ounces. She fed poorly and required gavage feeding on most occasions. A few attacks of pallor and cyanosis had occurred. On examination of the child there was obvious bilateral cataract. Examination of the heart demonstrated a loud harsh systolic bruit in the region of the second left intercostal space, with a suggestive continuous element. Lower down, a distinct to-and-fro murmur was heard, which might have been due to a separate lesion. Both femoral and radial pulses were present. The systolic blood pressure was 120 millimetres of mercury, and the diastolic blood pressure was 40 millimetres of mercury. A skiagram showed that the heart was large, but the contour was not particularly suggestive of patent *ductus arteriosus*. The lung fields were congested. Dr. Powell said that he regarded this infant as suffering from a patent *ductus arteriosus*, possibly with another lesion, such as a septal defect.

The third infant, aged four months, had been admitted to hospital with a diagnosis of upper respiratory tract infection and congenital heart disease. Although the infant was aged four months, the weight was only 12 pounds two ounces. On examination of the child, there was definite bronchiolitis, enlargement of the heart confirmed radiologically, and a very loud, apparently systolic murmur. Further examinations revealed that the murmur was heard best in the "surgical" area. All pulses were easily felt; and the systolic blood pressure was 120 millimetres of mercury, whilst the diastolic blood pressure could not be recorded. Considerable chest retraction was present during respiratory exercises, and it was thought that this was due to extreme cardiac enlargement. Although the diagnosis of patent *ductus arteriosus* was not a certain one, surgical exploration was carried out eight weeks after the baby had been admitted to hospital, and a large patent *ductus arteriosus* was found and ligated. After ligation the main murmur had vanished, but a short systolic bruit could still be heard in the pulmonary area. The baby had made good clinical improvement. The chest retraction had disappeared, and the weight showed a steady gain. However, the radiological appearance of the heart showed little improvement. Dr. Powell said that he was confident that the infant would show continued improvement, and he expected that the heart would become smaller.

In conclusion, Dr. Powell said that all three infants had large hearts, at an early age. Although the cardiac murmurs were not classical machinery murmurs in every case, an important feature was the fact that the murmurs were heard most clearly in the "surgical area"—high and to the left.[1]

DR. C. J. OFFICER BROWN said that until recently it had been considered that most cases of patent *ductus arteriosus* were compensatory to some other cardiac condition, but that belief was no longer accepted. He mentioned that at the Alfred Hospital, Melbourne, there had been only one death among 140 patients with patent *ductus arteriosus* treated surgically.

Dr. Officer Brown agreed with Dr. Russell Howard that parents who considered that their children were symptom-free were often pleasantly surprised at the improvement after surgery for patent *ductus arteriosus*. Every patent *ductus arteriosus* should be closed as soon as it was recognized, unless there were definite contraindications to surgery. Dr. Brown said that many adults aged from thirty to forty years had been referred to him with patent *ductus arteriosus* and congestive cardiac failure. He used Blalock's technique, and with that had had two recurrences only. He had divided the ductus 12 to 15 times, either from choice or from necessity. Division of the ductus was the ideal method in theory, but it was more hazardous, and the clamps could slip.

Referring to coarctation of the aorta, Dr. Brown said that he had operated on 38 patients suffering from that condition, with two deaths. One death was due to hæmorrhage from torn intercostal arteries, whilst the other was the result of a blood infection with a penicillin-resistant strain of *Staphylococcus aureus*. The anastomosis had come apart, and the patient had died.

Dr. Brown said that he had dealt with only three patients with aortic vascular rings. All three had presented with approximately the same symptom pattern as that shown by the child whom Dr. Russell Howard had presented. After surgical division, the stridor had disappeared immediately from one child, and in the other child it had lasted three months and then had disappeared. The third patient was a woman, aged forty-five years, whose main symptom had been dysphagia. That had improved following surgery. Dysphagia was the usual presenting symptom in adults because the trachea, being hard, was not easily compressed.

DR. C. H. FITTS said that he was impressed by the fact that many patients suffering from patent *ductus arteriosus* or coarctation of the aorta were very good physical specimens. He agreed that sometimes it was difficult to persuade parents that surgery was necessary. Dr. Fitts then demonstrated the case of a woman, aged twenty years, who had been diagnosed as having a patent *ductus arteriosus* with an aberrant right subclavian artery. Dr. Fitts exhibited skiagrams which led to this diagnosis. Recent operation had confirmed the abnormality.

Dr. J. M. GARDINER referred to two patients whose case reports he had presented at the September meeting of the Melbourne Pædiatric Society. Neither child (one was aged twelve years, the other fourteen years) had a typical continuous murmur of patent *ductus arteriosus*, yet the diagnosis had been confirmed by cardiac catheterization and later by surgery. The younger child had since developed a typical continuous murmur, probably because the ductus had become recanalized. The patient had a history of failing to thrive from the age of six to fourteen months. She had always been undersized, but after surgery she had gained weight and height rapidly. The other child since operation had gained ten pounds in six months, and was much improved clinically. Dr. Gardiner considered that cardiac catheterization was a justifiable investigation, but that technical difficulties precluded its use in small infants. Thoracotomy was an easier method of investigation.

DR. HOWARD WILLIAMS quoted the case history of an infant, aged seven months, who had presented with inspiratory and expiratory wheeze. Until then he had thrived well. It appeared that laryngeal stridor was unlikely because of the expiratory phase. A diagnosis of aortic vascular ring was made, and that was confirmed radiologically. It was considered that surgery was not indicated at that juncture. At the age of eighteen months the baby had pronounced stridor, and developed an epileptiform seizure. However, over a period of three and a half years the stridor had become progressively less, and now was heard only when the child became excited. Dr. Williams explained that stridor, when heard in both inspiratory and expiratory phases, was typical of tracheal obstruction, in contrast to the inspiratory stridor of laryngeal obstruction. That was an important differential feature. If the child was left alone, probably the stridor would diminish, and it might even disappear. As dysphagia had not developed at the age of five years, he might be quite symptom-free as an adult.

DR. KATE CAMPBELL suggested that malnutrition might be an ætiological factor in the development of congenital heart disease, and said that she could recall two patients with congenital cardiac disorders whose mothers had suffered from avitaminosis during pregnancy. Warkany had demonstrated that congenital deformities were produced in rats whose mothers had been fed on a vitamin-deficient diet.

[1] Subsequently, at operation, a patent *ductus arteriosus* was found in the first two cases described by Dr. Powell. In each infant the ductus was large, being approximately six millimetres in diameter compared to an aortic diameter of eight millimetres. In each infant the murmur vanished following surgery.

DR. J. H. COLEBATCH supported Dr. Campbell's statements. He said that during the first two to three weeks of pregnancy, before mothers knew that they were pregnant, they might neglect their diets. Nutrition should be adequate at the time of conception. Dr. Colebatch asked whether a child with a wheeze but no stridor should be investigated for an aortic vascular ring. That especially applied to a child suffering from prolonged asthma.

Dr. Powell, in reply to Dr. Colebatch, said that, if an aortic vascular ring was of any consequence, stridor should be present, or alternatively, in the older age group, some degree of dysphagia. Those were prerequisites for diagnosis, and it should be unnecessary to investigate a patient with an asthmatic wheeze for an aortic vascular ring. However, a patient with a minor degree of abnormality might be symptomless in the absence of excitement or respiratory tract infection.

DR. LAWRENCE STOKES said that surgery should be life-saving to the infants with patent *ductus arteriosus* whom Dr. Powell had demonstrated. There was no doubt that in small infants with that abnormality a systolic murmur alone might be present. Dr. Stokes quoted the case of a child whose patent *ductus arteriosus* had been treated surgically. The continuous machinery murmur had disappeared, but an early diastolic murmur had remained. That too had disappeared in three weeks. Dr. Stokes expressed an opinion that it had been due to a dilated pulmonary artery with resultant pulmonary regurgitation. After the pulmonary artery had become adapted and resumed its normal size, the diastolic murmur had vanished. Dr. Stokes mentioned that physical signs of other congenital heart defects could closely resemble those of patent *ductus arteriosus*.

DR. T. DUDLEY HAGGER asked whether Dr. Officer Brown would qualify, in reference to age, the statement "Every ductus should be operated upon when diagnosed".

Dr. Officer Brown, in reply, said that, in his opinion, there was no more risk in operating on an infant with patent *ductus arteriosus* than on a patient belonging to any other age group. In fact it might even be safer. A patent *ductus arteriosus* should not be closed as a routine procedure in patients twenty-five to thirty years of age, and certainly not in patients forty to fifty years of age. In those age groups surgery was indicated only when symptoms were present, or if there was congestive cardiac failure. It was known that some people with patent *ductus arteriosus* had lived to a "ripe old age".

Dr. Powell stated that he had observed 15 to 18 infants less than eighteen months of age who had presented with continuous bruits. They undoubtedly occurred. Dr. Powell then inquired why there should be such a variation in the degree of cardiac embarrassment at all age groups in patients with patent *ductus arteriosus*. He wondered if it could have any relationship to the angle of entry of the *ductus arteriosus* into the aorta, so that cardiac embarrassment increased as the line of the ductus approached that of the aortic arch. In concluding, Dr. Powell mentioned that Munro in 1907, at a post-mortem examination, had predicted that surgery would some day be the treatment of patent *ductus arteriosus*.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

TRANSACTIONS OF THE COLONY IN APRIL AND MAY, 1789.[1]

AN extraordinary calamity was now observed among the natives. Repeated accounts brought by our boats of finding bodies of the Indians in all the coves and inlets of the harbour caused the gentlemen of our hospital to procure some of them for the purposes of examination and anatomy. On inspection it appeared that the parties had died a natural death: pustules similar to those occasioned by smallpox were thickly spread on the bodies: but how a disease to which our former observations had led us to suppose them strangers could at once have introduced itself and could have spread so widely seemed inexplicable.(a) Whatever might be the cause, the existence of the malady could no longer be doubted. Intelligence was brought that an Indian family lay sick in a neighbouring cove: the governor attended by Arabanoo(b) and a surgeon went in a boat immediately to the spot. Here they found an old man stretched before a few lighted sticks and a boy of nine or ten years old pouring water on his head from a shell which he held in his hand: near them lay a little child dead and a little farther off its unfortunate mother: the body of the woman showed that famine superadded to disease had occasioned her death: eruptions covered the poor body from head to foot and the old man was so reduced that he could with difficulty be got into the boat.

[1] From "A Complete Account of the Settlement at Port Jackson", by Watkin Tench (1791). From the original in the Mitchell Library, Sydney.

(a) No solution of this difficulty had been given when I left the country in December, 1791. I can therefore only propose queries for the ingenuity of others to exercise itself upon: Is it a disease indigenous to the country? Did the French ships under Monsieur de Peyrouse introduce it? Let it be remembered that they had now been departed more than a year: and we had never heard of its existence on board of them. Had it travelled across the continent from its Western shore where Dampier or other European voyagers had formerly landed? Was it introduced by Mr. Cook? Did we give it birth here? No person among us had been afflicted with the disorder since we quitted the Cape of Good Hope seventeen months before. It is true that our surgeons had brought out variolous matter in bottles; but to infer that it was produced from this cause was a supposition so wild as to be unworthy of consideration.

(b) Arabanoo was a native who had a short time previously been seized at Manly and brought to Sydney Cove where he was considerately treated although under restraint. It was hoped that reports he would furnish his fellows of the mildness and indulgence with which he had been treated might improve relations with the natives and end the state of petty warfare then existing. He did in fact seem to become quite satisfied in his new circumstances and was allowed to roam at will without attempting to escape. However, he too contracted the prevailing epidemic and died in May, 1789, although "nothing which medical skill and unremitting attention could perform were left unexerted to mitigate his sufferings and prolong a life which humanity and affectionate concern towards his sick compatriots unfortunately shortened.

Correspondence.

THE FELLOWSHIP OF CHRISTIAN HEALING.

SIR: Readers of the journal must be grateful to Professor Osborne in his letter of the issue of April 17 for reminding them of the early Christian belief in demoniacal possession. Whether modern medicine has advanced sufficient evidence to make this belief no longer tenable is a matter for argument.

Yours, etc.,

KEVIN O'DAY.

33 Collins Street,
Melbourne, C.1,
April 23, 1954.

STAPHYLOCOCCAL INFECTIONS IN BABIES.

SIR: It was with interest that one read Dr. Clair Isbister's letter on staphylococcal infections in babies. Over the past twelve months we have seen a similar outbreak in this State which has emanated from maternity hospitals, and in which skin pustules and eye infections have predominated. Over this same period there has been an increased incidence of more serious complications, as neonatal osteomyelitis and staphylococcal pneumonia. This latter (which will be reported later) has occurred in long-stay cases in older children and adults in other hospitals. Like Dr. Isbister's cases, the organism in all these infections is penicillin-resistant clinically and *in vitro*, but responds to the tetracycline preparations. In the early cases there was a good response to chloramphenicol, but this has not been sustained in the later cases. The incidence of infection has been such that no one hospital can be incriminated.

The staphylococcus is widespread in the naso-pharynx of our community today. It is of nuisance value, and may be lethal, to many newborn babies. One would suggest that we give up paying lip service to the prevention of cross-infection and have installed enough running water inside

nurseries and enough gowns, masks, linen and disposable towels. The large two-storied traymobile wherein one baby lies against another as he is taken from nursery to the breast should be abolished. And would not these outbreaks of infection give a good case for "rooming in" of mother and child? Surely it is best to decentralize the possible sources of infection. Nurses should be taught not to handle their masks; or if they must, to wash their hands afterwards.

These are only a few well-known factors which may help in dealing with a preventible disease. And, sir, if preventible in hospitals, why not notifiable in this very susceptible age group?

Yours, etc.,

260 St. George's Terrace, Perth,
April 20, 1954.

JAMES WATSON.

TOBACCO SMOKING.

SIR: The following extract from Professor Max Muller's "Chips from a German Workshop" (1898) is interesting in these days when tobacco smoking is receiving so much attention.

Paul Hentzner published a book of travels in 1598. He had visited London in 1596 and "went to the theatres and to places Ursorum et Taurorum venationibus destinata, where bears and bulls, tied fast behind, were baited by bull-dogs. In these places, and everywhere, in fact, as our traveller says, when you meet with Englishmen, they use herba nicotiana, which they call by an American name, Tobaca or Paetum. The description deserves to be quoted in the original:

'Fistulæ in hunc finem ex argilla factæ orificio posteriori dictam herbam probe exsiccatam, ita ut in pulverem facile redigi possit, immittunt, et igne admoto accendunt, unde fumus ab anteriori parte ore attrahitur, qui per nares rursum, tamquam per infurnibulum exit, et phlegma ac capitis defluxiones magna copia secum educit.'"[1]

Yours, etc.,

Church Street,
Wollongong,
New South Wales.
March 30, 1954.

JOHN D. MAUDE.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 23, of April 14, 1954.

NAVAL FORCES OF THE COMMONWEALTH.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Appointments.—John Henry Begg and Anthony Sutherland Paton are appointed Surgeon Lieutenants with seniority in rank of 15th January, 1950, and 23rd November, 1953, respectively, dated 8th December, 1953, and 25th January, 1954, respectively. Ian Stuart Collins is appointed Surgeon Lieutenant, dated 10th February, 1954.

AUSTRALIAN MILITARY FORCES.

Royal Australian Army Medical Corps (Medical).

The Short Service Commission granted to 2/40135 Captain J. V. C. Brassil is extended until 19th May, 1955.

4/8036 Captain (provisionally) R. J. Pyne is appointed from the Citizen Military Forces, and to be Captain, 15th February, 1954, with a Short Service Commission for a period of one year.

The Short Service Commission granted to 3/40112 Captain (Temporary Major) G. A. Rutherford is extended until 26th February, 1954.

3/40112 Captain G. A. Rutherford relinquishes the temporary rank of Major and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (3rd Military District), 27th February, 1954.

Citizen Military Forces.

Northern Command: First Military District.

Royal Australian Army Medical Corps (Medical).—1/43710 Colonel K. B. Fraser, C.B.E., E.D., relinquishes the appointment of Deputy Director of Medical Services, Headquarters, Northern Command, and is placed upon the Retired List (1st Military District) with permission to retain his rank and wear the prescribed uniform, 29th March, 1954. 1/39001 Lieutenant-Colonel C. F. Marks, from command 11th Field Ambulance, is appointed Deputy Director of Medical Services, Headquarters, Northern Command, and to be Temporary Colonel, 29th March, 1954. 1/43715 Major T. R. Biggs is appointed to command 11th Field Ambulance, and to be Temporary Lieutenant-Colonel, 29th March, 1954.

Royal Australian Army Medical Corps (Medical).—The provisional rank of 1/39083 Captain R. Cantamessa is confirmed. 1/39152 Captain (provisionally) J. E. Mackay relinquishes the provisional rank of Captain and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (1st Military District) in the honorary rank of Captain, 15th December, 1952.

Eastern Command: Second Military District.

Royal Australian Army Medical Corps (Medical).—To be Captain (provisionally), 26th February, 1954: 2/61553 Kenelm John Witherington Stump.

Western Command: Fifth Military District.

Royal Australian Army Medical Corps (Medical).—5/32261 Captain M. Connaughton is appointed from the Reserve of Officers, and to be Temporary Major, 1st January, 1954.

Reserve Citizen Military Forces.

Royal Ausutralian Army Medical Corps (Medical): First Military District.

To be Honorary Captains.—Stanley Paul Stevens, 26th February, 1954, Peter Moore Smith and Eric Wilfred Lee, 1st March, 1954, and Grahame Frank Dixon, 9th March, 1954.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force.

Medical Branch.

Group Captain R. B. Davis (033026) is appointed to be Honorary Physician to His Excellency the Governor-General.

Squadron Leader W. L. Rait (033063) is appointed to a permanent commission, 1st December, 1953.

Squadron Leader A. S. Tredinnick (021945) is transferred from the Special Duties Branch with seniority as from 1st July, 1951.

The substantive rank of Squadron Leader A. S. Tredinnick (021945) is confirmed.

Squadron Leader J. F. Howell-Price (023025) is transferred to the Reserve, 6th February, 1954, on completion of his short-service commission.

Active Citizen Air Force.

Medical Branch.

No. 24 (City of Adelaide) Squadron.—Flight Lieutenant C. D. Swaine (041135) is transferred from the Reserve, 7th July, 1952.

Air Force Reserve.

Medical Branch.

The following former officer is appointed to a commission, 2nd December, 1953, with the rank of Flight Lieutenant: L. K. Rasmussen (025614).

The following are appointed to commissions with the rank of Flight Lieutenant: Frank Ivor Bishop (56387), 3rd November, 1953, William Carrick Heath (431773), 26th January, 1954.

[1] "They insert the said plant, thoroughly dried so that it can be easily reduced to a powder, in the rear opening of a pipe made of clay for the purpose, and light it by applying fire: from it smoke is drawn in by the mouth from the front part [of the pipe]; this goes out backwards through the nose, as much as through the smoking-funnel, and brings away with it phlegm and head secretions in great quantity."

Flight Lieutenant G. M. Bedbrook (257798) is promoted to the temporary rank of Squadron Leader, 15th December, 1953.

The provisional appointment of the following Pilot Officers is confirmed and they are promoted to the rank of Flight Lieutenant, 27th January, 1954: D. C. Swan (023627), R. J. Gaal (024217), R. H. Lumer (023628), P. W. Sundin (023629), I. L. Thompson (023630), P. C. M. Wilson (023632).

The appointment of Group Captain C. J. N. Leleu, O.B.E. (03178) as Honorary Physician to His Excellency the Governor-General is terminated.—(Ex. Min. No. 18—Approved 8th April, 1954.)

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Alteration of Lecture in Annual Subscription Course.

MEMBERS of the annual subscription course are advised that, owing to a change in his itinerary, Dr. Bradley Patten's lecture arranged for Tuesday, May 18, 1954, at 8.15 p.m., has been cancelled. This lecture entitled "Micromoving Pictures and Electrocardiographic Studies of Embryonic Heart Action" will now be held on Wednesday, June 9, 1954, at 8.15 p.m., in the Stawell Hall, 145 Macquarie Street, Sydney. The talk will be a combination of the following two lectures: "A Moving Picture Study of the First Heart Beats and the Beginning of the Embryonic Circulation" and "Changes in the Location of the Pacemaker and the Correlated Changes in the Electrocardiographic Pattern of the Embryonic Heart". Electrical recordings made by utilizing three-stage radio amplification show the steps in the development of an electrocardiogram of adult pattern, and the study as a whole gives the developmental background of the physiology of the adult sino-ventricular conduction system. Dr. Bradley Patten is Professor of Anatomy and Director of the Anatomy Department of Michigan School of Medicine, Ann Arbor, Michigan.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE following have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1950, as duly qualified medical practitioners (unless otherwise stated, the qualifications in each case are M.B., B.S., 1954, Univ. Sydney): Allman, John Gordon; Appleby, Bruce Robert; Asprey, Raymond Vincent; Bain, John Joseph; Baker, William Leslie; Barclay, William Arthur; Barnes, Jack Felstead; Bedville, Bryant Lewis; Bennett, Andrew Gordon Gregory; Bernstein, Louis; Blow, John Sydney; Boden, Richard William; Booth, Joan Cooper; Bowie, Marion Louie; Bracken, Barry Carsluith; Brady, Allan Jasper; Brake, Ian Terence; Brennan, Maurice Joseph; Brindal, Colin Frederick; Broughton, Peter William Stafford; Bull, Robert Russell; Burgess, Geoffrey Watkins; Cam, Donald Edmund; Campbell, Ian Alexander; Campbell, Mary Stewart; Cappe, Philip Francis; Carr, Edwin William; Carruthers, Malcolm Francis; Carter, Peter Geoffrey; Cass, Alexander Samuel; Chapman, Maxwell James; Christie, Gwenda Joy; Clarke, Frederick Brian Norton; Clarke, John Richmond; Clayton, Maxwell Richmond; Cleeve, Noel Pitt; Coleman, Roger Henry; Collins, Geoffrey Morison; Conaghan, John Peter; Connors, Kevin Patrick; Cooke, Samuel Lindsay; Coombes, Bruce William; Coyne, John Reynolds; Cranney, Kenneth Sidney; Crooks, John Yale; Cumming, William James; Cummings, Noel; Daniel, Ralph; Da Roza, Charles Bruno; Davies, William Edward Lewis; Dawes, Peter Douglas; Dearman, Patricia Heather; Deegan, Noel Errol; Deller, Donald John; Delves-Deffee, Edward Peter; Dobbie, John Alastair; Dixon, George Evan; Doust, Ian Stafford; Duncan, Howard; Dunlop, Ian Critchley; Egan, John Desmond; Ellis, Kenneth James; English, Cecil Hampshire; Facer, Kenneth James; Farrell, John Caldwell; Fealn, Leo Arthur; Fenwick, John; Firkin, Barry George; Florance, Brian; Florance, Ian Hugh; Fox, Mary Louise; Fraser, Ann Dale; Frith, Mary Eileen; Gaal, Robert James; Gardner, Thomas Joseph; Gemenis, Cedric Matthew; Gengos, Don Constantine; Georgeson, Laurence Edwin; Glover, Patricia Mary; Goldrick, Robert Brian; Graham, Charles Edmund; Haig, David

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 17, 1954.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	..	2(1)	..	1(1)	..	..	..	4
Amœbiasis	..	..	..	..	..	1	..	..	1
Ancylostomiasis	28	..	..	..	..	..	1	..	29
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	3	12(11)	8(4)	..	..	..	1	..	24
Diphtheria	5(4)	2(1)	2(2)	..	1	..	..	..	10
Dysentery (Bacillary)	..	3(2)	..	1(1)	2(1)	..	..	..	6
Encephalitis	1	..	..	..	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	4	14(5)	..	..	3(2)	..	..	..	21
Lead Poisoning	..	2(2)	..	..	..	..	..	..	2
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2(1)	..	..	..	..	..	2
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	1	..	..	..	..	1(1)	1	1	4
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	1(1)	..	..	..	..	..	..	1
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	15(6)	12(5)	3(2)	7(6)	14(8)	..	..	..	51
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	1(1)	..	..	9(7)	..	..	..	10
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	14(5)	29(18)	2(2)	4(4)	2(1)	1	..	..	52
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	..	..	..	..	1
Trachoma	..	..	..	..	2(1)	..	..	..	2
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	27(22)	25(19)	18(13)	8(7)	2(1)	2(1)	1	..	83
Typhoid Fever	1	..	1	..	..	..	..	..	2
Typhus (Flea-, Mite- and Tick-borne)	..	..	1(1)	1(1)	..	..	..	..	2
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Bruce; Harris, Leon Eugene; Harris, Michael James; Healey, Raymond Joseph; Hehir, John Desmond; Hickson, John Austin; Higgs, Ralph Crawford; Hill, Donald Winser; Hillman, Henry Samuel; Hodgkinson, David William Taylor; Holland, Victor Wallace; Hollings, Raymond Moulton; House, Harry; Huxtable, Bernard Ralston; Ireland, Desmond Joseph; Johnson, Peter Arundel; Jones, Brian Edmund; Jones, Keith Oswald Atkins; Jordan, Geoffrey Ellis; Kelly, William Mortimer; Killingback, Marcus James; Koorey, Stanley George; Lark, Elizabeth Anne; Leckie, Robert David; Ledermann, Ruth; Le Lievre, Leslie Ronald; Lilley, Leonard Bruce; Linegar, Valerie June; Linklater, Elizabeth; Lock, Raymond Junior; Lowe, Alice Marie; Lucas, Noel Alfred; Lumer, Rodney Hugh; McAlary, Robert Stratton; McCarthy, John Brian; McDonald, Anthony John; McDonald, Keith; McGrath, Philomena; McKessar, John Hubbard; McKinnery, Ambrose John; McRae, James; MacMahon, Robert Anthony; Mackay, Patricia Ann; Mansfield, Colin Harrison; Marshall, William Courtenay; Marshman, Raymond John; Massie, Hugh Hamon; Mayer, Beris Olwyn; Merrifield, Alan John; Meyers, John; Mishkel, Maurice Alan; Mitchell, Henry James; Moulton, John Egan; Munro, Frank Edward; Murphy, Arthur James O'Grady; Musgrave, Paul Anthony Baker; Nelson, David Yeates; Newlinds, John Stuart; Ng, Yook Wee; Nicholson, Margaret Faith; Norington, Bradney William; North, Brian Keith; Oeding, Francis Joseph; Paczowsky, Johannes Robert; Patterson, Robert William; Payne, William Harold; Pelly, Anthony D'Arcy; Pfeifer, Albert; Posney, Kazimierz; Raine, June Marion; Rankin, James Gerald D'Arcy; Redhead, Harris Frank; Rivett, Howard Maitland; Roberts, John; Rosler, Alice Mary; Rugless, Eric; Sanderson, Erle Jack; Sarfaty, Gordon Alfred; Saxton, John; Scott, Andrew Murray; Scott, Ellison; Seaton, Douglass George; Segall, Margot; Segelov, Phillip Myer; Seidel, Ulric Paul; Selby, Theodore; Sharrock, Keith Douglas; Shearman, Brian Thomas; Silverton, Robert Peter; Skinner, Haydn French; Smith, Robert Gordon; Spencer, Owen Lisle; Sproule, Brian Creighton; Stange, Fay Joan; Stark, Harry; Storey, Gilbert Norman Bruce; Sundin, Paul William; Swan, David Chetham; Sweetapple, William Edmond; Talley, Nicholas Alexander; Taylor, Hugh Edmund Carlyle; Tebbutt, Robert John Limbury; Thew, Ian Phillip; Thompson, Ian Lyall; Tomasiello, Patrick Peter; Tomlin, Alwynne Dorothy; Tooth, Maxwell John; Travers, Desmond Benedict; Trief, Miriam Margaret; Velens, Victoria Lydia; Verge, John Mackay; Vickers, John William; Waddy, Phyllis Mary; Wagner, Gerhard Richard; Walker, William Downing; Wansey, Richard Barry; Ward, James Francis; Warren, Agnes Grace; Wheeler, Valmae June Mackay; Whish, Keith Milroy; White, David Ogilvie; Wilken, Judeth Lawes; Wilson, Kenneth Peter; Wilson, Peter Charles McLeod; Wingfield, John Douglas; Woodforde, John Marcus; Woolridge, John David; Wright, Jean; Young, Ailsa Margaret; Young, Richard Vousden; Zorbas, John; Ewing, Donald Peter, M.B., 1954 (Univ. Sydney); Gray, Ronald McKay, M.B., 1954 (Univ. Sydney).

The following additional qualifications have been registered: Davis, Florence May (M.B., B.S., 1948, Univ. Sydney), D.C.P., 1953, Univ. Sydney; Evans, Cyril Percival Victorious (M.B., B.S., 1945, D.T.M., 1946, Univ. Sydney), M.R.C.P. (London), 1953.

QUEENSLAND.

THE following have been registered, pursuant to the provisions of *The Medical Acts*, 1939-1948, as duly qualified medical practitioners: Jones, Anthony Charles, M.B., B.S., 1951 (Univ. Sydney); Brown, Bruce Alexander, M.B., B.S., 1952 (Univ. Sydney); Finney, Dallas, M.B., B.S., 1952 (Univ. Sydney); Cunningham, Angus Brian, M.B., B.S., 1953 (Univ. Sydney); Hancock, John Owen, M.B., B.S., 1952 (Univ. Adelaide); Wilson, Kenneth Peter, M.B., B.S., 1954 (Univ. Sydney).

The following additional qualification has been registered: Guastalla, Piero Bruto, D.G.O. (Trinity College, Dublin), 1950, D.Obst., R.C.O.G. (London), 1950, M.R.C.O.G. (London), 1953.

Deaths.

THE following deaths have been announced:

DERAVIN.—Garnet Wesley Deravin, on April 15, 1954, at North Balwyn, Victoria.

LEY.—Charles Pattinson Ley, on April 22, 1954, at Sydney.

Medical Appointments.

Dr. R. D. Carman has been appointed medical superintendent of the Bedford Park Sanatorium, South Australia.

Dr. G. F. Bradfield has been appointed government medical officer at Julia Creek, Queensland.

Dr. C. Checchi has been appointed a commissioner of the Shire of Ararat Waterworks Trust, Victoria.

Dr. A. N. Turner has been appointed a part-time officer of health in South Australia.

Dr. Babette Josephine Worling has been appointed to the School Medical Service in the Department of Public Health of New South Wales.

Dr. J. A. C. Brassil has been appointed to the Division of Mental Hygiene in the Department of Public Health of New South Wales.

Diary for the Month.

MAY 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAY 14.—Queensland Branch, B.M.A.: Council Meeting.
MAY 17.—Victorian Branch, B.M.A.: Finance Subcommittee.
MAY 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.
side Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Tasmania: Part-time specialist appointments for the north-west coast of Tasmania.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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